```
=> d his full

     (FILE 'HOME' ENTERED AT 19:49:48 ON 04 JAN 2006)

     FILE 'REGISTRY' ENTERED AT 19:50:10 ON 04 JAN 2006
                E ALT 711/CN
L1            2 SEA "ALT 711"/CN
                D L1 1-2

     FILE 'HCAPLUS, USPATFULL, USPAT2' ENTERED AT 19:51:19 ON 04 JAN 2006
L2           56 SEA L1
L3           51 DUP REM L2 (5 DUPLICATES REMOVED)
                D L3 ABS CBIB HITRN 1-51
L4           17 SEA L3 AND HYPERTENS?
                D L4 ABS CBIB KWIC HITRN 1-17
L5         6447 SEA HYDROCHLOROTHIAZID?
L6            3 SEA L5 AND L3
                D L6 ABS CBIB KWIC HITRN 1-3
L7          725 SEA L5 AND SYSTOL? AND HYPERTENS?
L8          602 SEA L5 AND SYSTOL?(P) HYPERTENS?
                D L8 CBIB KWIC 595-602
L9          796 SEA ISOLAT?(P) SYSTOL?(P) HYPERTENS?
                D L9 KWIC 1-5
L10         318 SEA ISOLAT?(3A) SYSTOL?(4A) HYPERTENS?
                D L10 KWIC 1-5
L11          77 SEA L5 AND L10
                D L11 KWIC 70-77
                D L11 CBIB 72

     FILE 'STNGUIDE' ENTERED AT 20:08:41 ON 04 JAN 2006

     FILE 'HCAPLUS, USPATFULL, USPAT2' ENTERED AT 20:10:30 ON 04 JAN 2006
L12          37 SEA L5(P) L10
L13          37 DUP REM L12 (0 DUPLICATES REMOVED)
                D L13 CBIB 1-37

     FILE 'STNGUIDE' ENTERED AT 20:15:24 ON 04 JAN 2006

     FILE 'STNGUIDE' ENTERED AT 20:18:33 ON 04 JAN 2006


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:    3 JAN 2006  HIGHEST RN 871080-87-4
     DICTIONARY FILE UPDATES:   3 JAN 2006  HIGHEST RN 871080-87-4

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     ************************************************************
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*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                    *
**********************************************************************

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for details.

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predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE HCAPLUS

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FILE COVERS 1907 - 4 Jan 2006  VOL 144 ISS 2
FILE LAST UPDATED: 3 Jan 2006  (20060103/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 3 Jan 2006 (20060103/PD)
FILE LAST UPDATED: 3 Jan 2006 (20060103/ED)
HIGHEST GRANTED PATENT NUMBER: US6983486
HIGHEST APPLICATION PUBLICATION NUMBER: US2005289677
CA INDEXING IS CURRENT THROUGH 3 Jan 2006 (20060103/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 3 Jan 2006 (20060103/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2005

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<
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>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 3 Jan 2006 (20060103/PD)
FILE LAST UPDATED: 3 Jan 2006 (20060103/ED)
HIGHEST GRANTED PATENT NUMBER: US2004192897
HIGHEST APPLICATION PUBLICATION NUMBER: US2005289660
CA INDEXING IS CURRENT THROUGH 3 Jan 2006 (20060103/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 3 Jan 2006 (20060103/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2005

USPAT2 is a companion file to USPATFULL. USPAT2 contains full text of the latest US publications, starting in 2001, for the inventions covered in USPATFULL. USPATFULL contains full text of the original published US patents from 1971 to date and the original applications from 2001. In addition, a USPATFULL record for an invention contains a complete list of publications that may be searched in standard search fields, e.g., /PN, /PK, etc.

USPATFULL and USPAT2 can be accessed and searched together through the new cluster USPATALL. Type FILE USPATALL to enter this cluster.

Use USPATALL when searching terms such as patent assignees, classifications, or claims, that may potentially change from the earliest to the latest publication.

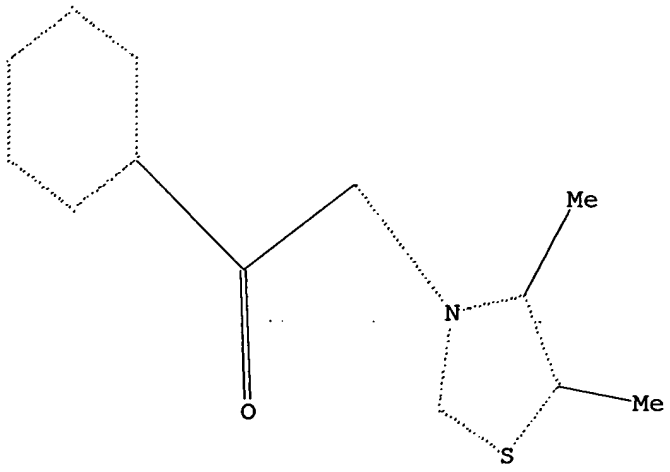
FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Dec 30, 2005 (20051230/UP).

=>

FILE 'STNGUIDE' ENTERED AT 17:58:21 ON 04 JAN 2006

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Dec 30, 2005 (20051230/UP).

=> d que stat
L1 STR



Structure attributes must be viewed using STN Express query preparation.
L3 40 SEA FILE=REGISTRY SSS FUL L1
L4 1 SEA FILE=REGISTRY (HYDROCHLOROTHIAZID/CN OR HYDROCHLOROTHIAZIDE /CN)
L5 3 SEA L3 AND L4
L6 2 DUP REM L5 (1 DUPLICATE REMOVED)

=> d his full

(FILE 'HOME' ENTERED AT 17:52:15 ON 04 JAN 2006)

FILE 'STNGUIDE' ENTERED AT 17:52:21 ON 04 JAN 2006
SET LINE 250
SET DETAIL OFF

FILE 'HOME' ENTERED AT 17:52:24 ON 04 JAN 2006
SET LINE LOGIN
SET DETAIL LOGIN

FILE 'REGISTRY' ENTERED AT 17:52:33 ON 04 JAN 2006
L1 STRUCTURE UPLOADED
D L1
L2 0 SEA SSS SAM L1
L3 40 SEA SSS FUL L1

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     FILE 'HCAPLUS, USPATFULL, USPAT2' ENTERED AT 17:55:45 ON 04 JAN 2006

     FILE 'REGISTRY' ENTERED AT 17:56:07 ON 04 JAN 2006
                E HYDROCHLOROTHIAZIDE/CN
L4              1 SEA (HYDROCHLOROTHIAZID/CN OR HYDROCHLOROTHIAZIDE/CN)
                D L4 1-2

     FILE 'HCAPLUS, USPATFULL, USPAT2' ENTERED AT 17:56:57 ON 04 JAN 2006
L5              3 SEA L3 AND L4
L6              2 DUP REM L5 (1 DUPLICATE REMOVED)
                D L6 ABS CBIB HITSTR HITRN 1-2

     FILE 'STNGUIDE' ENTERED AT 17:58:21 ON 04 JAN 2006
                D QUE STAT


     FILE HOME

     FILE STNGUIDE
     FILE CONTAINS CURRENT INFORMATION.
     LAST RELOADED: Dec 30, 2005 (20051230/UP).

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:     3 JAN 2006  HIGHEST RN 871080-87-4
     DICTIONARY FILE UPDATES:    3 JAN 2006  HIGHEST RN 871080-87-4

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     ************************************************************
     *                                                          *
     * The CA roles and document type information have been removed from *
     * the IDE default display format and the ED field has been added,   *
     * effective March 20, 2005.  A new display format, IDERL, is now    *
     * available and contains the CA role and document type information. *
     *                                                          *
     ************************************************************

     Structure search iteration limits have been increased.  See HELP SLIMITS
     for details.

     REGISTRY includes numerically searchable data for experimental and
     predicted properties as well as tags indicating availability of
     experimental property data in the original document.  For information
     on property searching in REGISTRY, refer to:

     http://www.cas.org/ONLINE/UG/regprops.html

     FILE HCAPLUS
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FILE COVERS 1907 - 4 Jan 2006 VOL 144 ISS 2
FILE LAST UPDATED: 3 Jan 2006 (20060103/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 3 Jan 2006 (20060103/PD)
FILE LAST UPDATED: 3 Jan 2006 (20060103/ED)
HIGHEST GRANTED PATENT NUMBER: US6983486
HIGHEST APPLICATION PUBLICATION NUMBER: US2005289677
CA INDEXING IS CURRENT THROUGH 3 Jan 2006 (20060103/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 3 Jan 2006 (20060103/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 3 Jan 2006 (20060103/PD)
FILE LAST UPDATED: 3 Jan 2006 (20060103/ED)
HIGHEST GRANTED PATENT NUMBER: US2004192897
HIGHEST APPLICATION PUBLICATION NUMBER: US2005289660

CA INDEXING IS CURRENT THROUGH 3 Jan 2006 (20060103/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 3 Jan 2006 (20060103/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2005

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USPATFULL and USPAT2 can be accessed and searched together through the new cluster USPATALL. Type FILE USPATALL to enter this cluster.

Use USPATALL when searching terms such as patent assignees, classifications, or claims, that may potentially change from the earliest to the latest publication.

=>

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E1            1     ALT RNA POLYMERASE ADP-RIBOSYLASE (BACTERIOPHAGE AEH1 GENE A
                    LT)/CN
E2            1     ALT-2 MONOCLONAL ANTIBODY/CN
E3            0 --> ALT-711/CN
E4            1     ALT. ANKYRIN (VARIANT 2.2) (HUMAN CLONE PANK(58, 42B, 37, 15
                    , 1B, 22))/CN
E5            1     ALTA 2002/CN
E6            1     ALTA 2341/CN
E7            1     ALTABACTINA/CN
E8            1     ALTABACTINE/CN
E9            1     ALTACE/CN
E10           1     ALTACET/CN
E11           1     ALTACITE/CN
E12           1     ALTACITE PLUS/CN

=> e alt711/cn
E1            1     ALT-2 MONOCLONAL ANTIBODY/CN
E2            1     ALT. ANKYRIN (VARIANT 2.2) (HUMAN CLONE PANK(58, 42B, 37, 15
                    , 1B, 22))/CN
E3            0 --> ALT711/CN
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E5            1     ALTA 2341/CN
E6            1     ALTABACTINA/CN
E7            1     ALTABACTINE/CN
E8            1     ALTACE/CN
E9            1     ALTACET/CN
E10           1     ALTACITE/CN
E11           1     ALTACITE PLUS/CN
E12           1     ALTACONITINE/CN

=> e alt 711/cn
E1            1     ALT 462/CN
E2            1     ALT 486/CN
E3            2 --> ALT 711/CN
E4            1     ALT 8794/CN
E5            1     ALT 946/CN
E6            1     ALT RNA POLYMERASE ADP-RIBOSYLASE (BACTERIOPHAGE AEH1 GENE A
                    LT)/CN
E7            1     ALT-2 MONOCLONAL ANTIBODY/CN
E8            1     ALT. ANKYRIN (VARIANT 2.2) (HUMAN CLONE PANK(58, 42B, 37, 15
                    , 1B, 22))/CN
E9            1     ALTA 2002/CN
E10           1     ALTA 2341/CN
E11           1     ALTABACTINA/CN
E12           1     ALTABACTINE/CN

=> s e3
L7            2 "ALT 711"/CN

=> d l7 1-2

L7   ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2006 ACS on STN
RN   341028-37-3  REGISTRY
ED   Entered STN:  14 Jun 2001
CN   Thiazolium, 4,5-dimethyl-3-(2-oxo-2-phenylethyl)-, chloride (9CI)  (CA
     INDEX NAME)
OTHER NAMES:
```
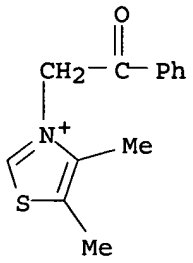

CN Alagebrium chloride
CN **ALT 711**
MF C13 H14 N O S . Cl
SR CAS Client Services
LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, CASREACT, IMSDRUGNEWS, IMSRESEARCH, IPA, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
CRN (393121-34-1)

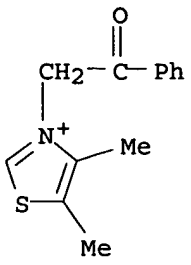


● Cl⁻

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

16 REFERENCES IN FILE CA (1907 TO DATE)
16 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L7 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2006 ACS on STN
RN 181069-80-7 REGISTRY
ED Entered STN: 20 Sep 1996
CN Thiazolium, 4,5-dimethyl-3-(2-oxo-2-phenylethyl)-, bromide (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **ALT 711**
MF C13 H14 N O S . Br
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, IMSRESEARCH, PHAR, PROUSDDR, SYNTHLINE, TOXCENTER, USPATFULL
CRN (393121-34-1)



20 REFERENCES IN FILE CA (1907 TO DATE)
20 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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FILE 'HCAPLUS' ENTERED AT 19:51:19 ON 04 JAN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPATFULL' ENTERED AT 19:51:19 ON 04 JAN 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 19:51:19 ON 04 JAN 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

=> d his

     (FILE 'HOME' ENTERED AT 19:49:48 ON 04 JAN 2006)

     FILE 'REGISTRY' ENTERED AT 19:50:10 ON 04 JAN 2006
                E ALT 711/CN
L1            2 S E3

     FILE 'HCAPLUS, USPATFULL, USPAT2' ENTERED AT 19:51:19 ON 04 JAN 2006

=> s l1
L2          56 L1

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3           51 DUP REM L2 (5 DUPLICATES REMOVED)

=> d l3 abs cbib hitrn 1-51

L3   ANSWER 1 OF 51  HCAPLUS  COPYRIGHT 2006 ACS on STN
AB   The invention relates to the discovery that levels of collagen and elastin
     can be modulated by changing the flux through the Amadori Pathway and that
     copper containing compds. and complexes inhibit the enzyme
     fructosamine-3-kinase.  The present invention includes a method of
     decreasing desmosine levels in a mammal in need thereof, the method
     comprising administering to a mammal a composition comprising an inhibitor of
     the Amadorase pathway.  In one embodiment, the inhibitor inhibits
     fructosamine kinase.  In another embodiment, the composition further comprises
     an inhibitor of 3-deoxyglucosone (3DG).  In one aspect, the mammal is a
     human.  In another aspect, a human has at least one disease selected from
     the group consisting of diabetes and lung fibrosis.
2005:961945   Document Number 143:260404  Fructosamine 3 kinase and the formation
     of collagen and elastin.  Tobia, Annette; Kappler, Francis; Schwartz,
     Michael L. (Dynamis Therapeutics, Inc., USA).  PCT Int. Appl. WO
     2005079463 A2 20050901, 196 pp.  DESIGNATED STATES: W:  AE, AG, AL, AM,
     AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE,
     DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN,
     IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
     MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
     SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA,
     ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR,
     GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR.
     (English).  CODEN: PIXXD2.  APPLICATION: WO 2005-US5082 20050217.
     PRIORITY: US 2004-2004/PV54503U 20040217; US 2004-2004/PV545036 20040217.
IT   181069-80-7
```

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modulators of fructosamine 3 kinase and the formation of collagen and elastin in relation to 3-deoxyglucosone toxicity and disease treatment)

L3 ANSWER 2 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB A method for delivering polymerized therapeutic agents and their compns. are disclosed. The various polymers take advantage of the functional domains found in a variety of therapeutic agents. The polymerized therapeutic agent compns. are prepared by covalently linking the agent to a biocompatible backbone either directly or through backbone conjugates/monomers. The polymerized therapeutic agent compns. of the invention have highly desirable properties, which make them particularly well suited for use in biol. and biomedical applications. An example is polyaspartate with rofecoxib-OH derivative ester side chains.

2005:29217 Document Number 142:141234 Delivering polymerized therapeutic agent compositions. Waugh, Jacob; Razavi, Mahmood; Rhee, Ceron; Bryant, Clifford (Polycord, Inc., USA). PCT Int. Appl. WO 2005002597 A1 20050113, 79 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US21453 20040702. PRIORITY: US 2003-2003/PV48507U 20030702; US 2004-2004/884226 20040702.

IT **181069-80-7**, ALT-711
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(delivering polymerized therapeutic agent compns.)

L3 ANSWER 3 OF 51 USPATFULL on STN

AB In one embodiment, the present invention relates to compounds and compositions including pharmaceutical compositions containing the compounds and associated methods that uncouple sugar-mediated coupling of proteins, lipids, nucleic acids, and other biomaterials, and any combination thereof. In another embodiment, the compositions and associated methods have utility in vivo to reduce the deleterious effects of sugar-mediated coupling processes in an organism, when the organism is exposed to the compound or composition internally, by ingestion, transdermal application, or other means. In yet another embodiment, the compositions and associated methods are useful for the ex-vivo treatment of organs, cells and tissues and external treatment of hair, nails and skin to rejuvenate them by changing deformability and increase the tissue diffusion coefficient. In a further embodiment, the present invention relates to novel compounds and pharmaceutical compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

2005:281557 Method and composition for rejuvinating cells, tissues organs, hair and nails.
Ulrich, Peter C., Portland, OR, UNITED STATES
Fang, Sheng Ding, Mount Kisco, NY, UNITED STATES
Brines, Michael L., Woodbridge, CT, UNITED STATES
Xie, Qiao-Wen, Yonkers, NY, UNITED STATES
Cerami, Anthony, Sleepy Hollow, NY, UNITED STATES

US 2005245512 A1 20051103
APPLICATION: US 2005-175098 A1 20050705 (11)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **341028-37-3**
(preparation of azoles, azines and salts thereof for rejuvenating cells, tissues, organs, hair and nails)

L3 ANSWER 4 OF 51 USPATFULL on STN
AB The invention relates to the discovery that 3-deoxyglucosone (3DG) and other alpha-dicarbonyl sugars associated diseases and disorders are present and produced in the skin. Further, the invention relates to the discovery that amadorase, an enzyme that mediates 3DG synthesis, is also present in the skin. Thus, the invention further relates to methods of inhibiting production and function of 3-deoxyglucosone and other alpha-dicarbonyl sugars in skin thereby treating or prevention various diseases, disorders or conditions. Additionally, the invention relates to treatment of various diseases, disorders or conditions associated with or mediated by oxidative stress since 3DG induces ROS and AGEs, which are associated with the inflammatory response caused by oxidative stress.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
2005:183988 3-deoxyglucosone and skin.
Tobia, Annette, Wyndmoor, PA, UNITED STATES
Kappler, Francis, Philadelphia, PA, UNITED STATES
Dynamis Therapeutics, Inc. (U.S. corporation)
US 2005159383 A1 20050721
APPLICATION: US 2004-966967 A1 20041015 (10)
PRIORITY: US 2002-373103P 20020417 (60)
US 2002-392530P 20020627 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **181069-80-7**
(inhibition of 3-deoxyglucosone and α-dicarbonyl sugars in skin and therapeutic uses for oxidative stress related diseases)

L3 ANSWER 5 OF 51 USPATFULL on STN
AB A method for delivering polymerized therapeutic agents and their compositions are disclosed. The various polymers take advantage of the functional domains found in a variety of therapeutic agents. The polymerized therapeutic agent compositions are prepared by covalently linking the agent to a biocompatible backbone either directly or through backbone conjugates/monomers. The polymerized therapeutic agent compositions of the invention have highly desirable properties, which make them particularly well suited for use in biological and biomedical applications.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
2005:86963 Method for delivering polymerized therapeutic agent compositions and compositions thereof.
Waugh, Jacob, Palo Alto, CA, UNITED STATES
Razavi, Mahmood, Menlo Park, CA, UNITED STATES
Rhee, Ceron, Saratoga, CA, UNITED STATES
Bryant, Clifford, Millbrae, CA, UNITED STATES
Polycord, Inc., Stanford, CA (U.S. corporation)
US 2005074425 A1 20050407

APPLICATION: US 2004-884226 A1 20040702 (10)
PRIORITY: US 2003-485076P 20030702 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **181069-80-7**, ALT-711
(delivering polymerized therapeutic agent compns.)

L3 ANSWER 6 OF 51 USPATFULL on STN
AB Provided are compounds of the formula (and pharmaceutically acceptable salts thereof): ##STR1##

wherein:

R is hydrogen, methyl, hydroxymethyl or α-hydroxyethyl;

R.sup.1 and R.sup.2 are independently selected from hydrogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 hydroxyalkyl, C.sub.3-C.sub.8 cycloalkyl, C.sub.1-C.sub.6 alkenyl, C.sub.1-C.sub.6 alkynyl, amino, monoalkylamino, dialkylaminoalkyl, and pyrrolidin-1-ylalkyl; and Y is selected from the group consisting of C.sub.1-C.sub.6 alkyl, substituted and unsubstituted aryl; with the provisos that: (a) if Y is aryl, then at least one of R.sup.1 and R.sup.2 is other than hydrogen, and (b) if R.sup.2 is hydrogen R.sup.1 is other than methyl.

Also provided are pharmaceutical compositions containing the compounds, and methods for the preparation of the compounds. The compounds are useful, among other things, as prodrugs which can be converted under acidic conditions to thiazolium agents. The compounds can be administered to mammals, including humans, for treatment of various indications.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
2005:17345 Dihydrothiazine prodrugs of thiazolium agents.
Reinhard, Emily, Ridgewood, NJ, UNITED STATES
Katten, Elliot, Flushing, NY, UNITED STATES
US 2005014747 A1 20050120
APPLICATION: US 2004-824848 A1 20040415 (10)
PRIORITY: US 2003-463807P 20030418 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **341028-37-3**
(preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for hypertension, diastolic dysfunction, heart failure, and reduced vascular compliance)

L3 ANSWER 7 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN
AB A review. Prolonged hyperglycemia, dyslipidemia and oxidative stress in diabetes result in the production and accumulation of AGEs. It is now clear that AGEs contribute to the development and progression of cardiovascular disease in diabetes, as well as other complications. AGEs are thought to act through receptor-independent and dependent mechanisms to promote vascular damage, fibrosis and inflammation associated with accelerated atherogenesis. As a result, novel therapeutic agents to reduce the accumulation of AGEs in diabetes have gained interest as potential cardioprotective approaches. A variety of agents have been developed which are examined in detail in this review. These include aminoguanidine, ALT-946, pyridoxamine, benfotiamine, OPB-9195, alagebrium chloride,

N-phenacylthiazolium bromide and LR-90. In addition, it has been demonstrated that a number of established therapies have the ability to reduce the accumulation of AGEs in diabetes including ACE inhibitors, angiotensin receptor antagonists, metformin, peroxisome proliferators receptor agonists, metal chelators and some antioxidants. The fact that many of these inhibitors of AGEs are effective in exptl. models, despite their disparate mechanisms of action, supports the keystone role of AGEs in diabetic vascular damage. Nonetheless, the clin. utility of AGE inhibition remains to be firmly established. Optimal metabolic and blood pressure control, that is achieved early and sustained indefinitely, remains the best recourse for inhibition of AGEs until more specific interventions become a clin. reality.

2005:574270 Document Number 143:241179 The role of AGEs and AGE inhibitors in diabetic cardiovascular disease. Thomas, M. C.; Baynes, J. W.; Thorpe, S. R.; Cooper, M. E. (Danielle Alberti Memorial Centre for Diabetes Complications, Baker Medical Research Institute, Melbourne, Australia). Current Drug Targets, 6(4), 453-474 (English) 2005. CODEN: CDTUAU. ISSN: 1389-4501. Publisher: Bentham Science Publishers Ltd..

IT **341028-37-3**, Alagebrium chloride
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(role of AGEs and AGE inhibitors in diabetic cardiovascular disease)

L3 ANSWER 8 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

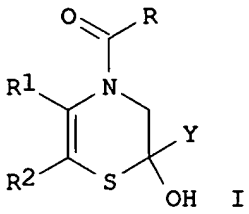
AB A review. The research of Little et al. entitled "The effect of alagebrium chloride (ALT-711), a novel glucose cross-link breaker, in the treatment of elderly patients with diastolic heart failure" is reviewed with commentary and refs. Little et al. step outside the heart failure (HF) box by testing a novel compound designed to specifically target increases in arterial and left ventricular (LV) stiffness, perturbations proposed as key to the pathogenesis of diastolic HF (DHF). The novel elements of this strategy lie in the fact that the therapy tested is specifically linked to the proposed pathogenesis of DHF, is not a recognized neurohumoral antagonist, and has not been tested in systolic HF. Alagebrium purportedly breaks crosslinks formed between collagen fibers as the result of the long term accumulation of advanced glycation end-products on collagen and other long-lived proteins.

2005:289132 Document Number 143:145360 Treating diastolic heart failure with AGE crosslink breakers: Thinking outside the heart failure box. Redfield, Margaret M. (From the Cardiorenal Research Laboratory, Mayo Clinic College of Medicine, Rochester, MN, USA). Journal of Cardiac Failure, 11(3), 196-199 (English) 2005. CODEN: JCFAF9. ISSN: 1071-9164. Publisher: Elsevier Inc..

IT **341028-37-3**, ALT 711
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT 711; preclin. and early clin. data indicate ALT-711 may be effective in DHF through breaking crosslinks formed between collagen fibers as result of long term accumulation of AGE on collagen and other long-lived proteins)

L3 ANSWER 9 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

GI



I

AB The authors prepared thiazine compds. I [R = H, Me, HOCH2, MeCHOH; R1, R2 = H, C1-C6 alkyl, C1-C6 hydroxyalkyl, C3-C8 cycloalkyl, C1-C6 alkenyl, C1-C6 alkynyl, amino, monoalkylamino, dialkylaminoalkyl, pyrrolidin-1-ylalkyl; Y = C1-C6 alkyl, substituted and unsubstituted aryl; with the provisos that: (a) if Y = aryl, then at least one of R1 and R2 is other than H, and (b) if R2 = H, R1 = not Me] (and pharmaceutically acceptable salts thereof). For example, 4,5-dimethyl-3-(2-oxo-2-phenylethyl)thiazolium chloride was reacted with NaOH to give I (R = H, R1 = R2 = Me, Y = Ph). The compds. are useful, among other things, as prodrugs which can be converted under acidic conditions to thiazolium agents. The compds. can be administered to mammals, including humans, for treatment of various indications including hypertension, reduced vascular compliance, diastolic dysfunction, heart failure, and isolated systolic hypertension.

2004:927187 Document Number 141:395566 Preparaton of dihydrothiazine prodrugs of thiazolium agents. Reinhard, Emily; Katten, Elliot (Alteon, Inc., USA). PCT Int. Appl. WO 2004094396 A2 20041104, 40 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US11984 20040416. PRIORITY: US 2003-PV463807 20030418; US 2004-824848 20040415.

IT **341028-37-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for hypertension, diastolic dysfunction, heart failure, and reduced vascular compliance)

L3 ANSWER 10 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB An ophthalmic formulation is provided for the prevention and treatment of adverse ocular conditions, including presbyopia, arcus senilis, age-related macular degeneration, and other conditions associated with aging. The formulation is also useful in the prevention and treatment of other adverse ocular conditions such as those associated with oxidative and/or free radical damage within the eye; these conditions can involve a condition, disease, or disorder of the cornea, retina, lens, sclera, anterior segment, or posterior segment of the eye. In one embodiment, the formulation contains 0.6 weight% of a biocompatible chelating agent, an ophthalmic permeation enhancer such as methylsulfonylmethane (MSM), an anti-aging agent, i.e., a compound that serves to reduce the presence of advanced glycation end-products (AGEs) in the eye, and an ophthalmic carrier suited to the particular formulation type (e.g., eye drops or ointments). Preferred components of the formulation are multifunctional

and naturally occurring. Thus, eyedrops contained water 91.74, MSM 4.95, disodium EDTA 2.39, and L-carnosine 0.92%.

2004:565111 Document Number 141:111583 Ophthalmic formulations containing chelates and enhancers for the prevention and treatment of eye disorders. Bhushan, Rajiv (Chakshu Research, Inc., USA). PCT Int. Appl. WO 2004058289 A1 20040715, 47 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US41141 20031222. PRIORITY: US 2002-2002/PV43584U 20021220; US 2003-2003/PV506474 20030926.

IT **181069-80-7 341028-37-3**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ophthalmic formulations containing chelates and enhancers for prevention and treatment of eye disorders)

L3 ANSWER 11 OF 51 USPATFULL on STN

AB An ophthalmic formulation is provided for the prevention and treatment of adverse ocular conditions, including presbyopia, arcus senilis, age-related macular degeneration, and other conditions associated with aging. The formulation is also useful in the prevention and treatment of other adverse ocular conditions such as those associated with oxidative and/or free radical damage within the eye; these conditions can involve a condition, disease, or disorder of the cornea, retina, lens, sclera, anterior segment, or posterior segment of the eye. In one embodiment, the formulation contains at least 0.6 weight % of a biocompatible chelating agent, an effective permeation enhancing amount of an ophthalmic permeation enhancer such as methylsulfonylmethane (MSM), an anti-AGE agent, i.e., a compound that serves to reduce the presence of advanced glycation endproducts (AGEs) in the eye, and a pharmaceutically acceptable ophthalmic carrier suited to the particular formulation type (e.g., eye drops or ointments). Preferred components of the formulation are multifunctional and naturally occurring.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

2004:177904 Ophthalmic formulation for the prevention and treatment of adverse ocular conditions, particularly those associated with the aging eye. Bhushan, Rajiv, Palo Alto, CA, UNITED STATES
US 2004137068 A1 20040715
APPLICATION: US 2003-744524 A1 20031222 (10)
PRIORITY: US 2002-435849P 20021220 (60)
US 2003-506474P 20030926 (60)
DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **181069-80-7 341028-37-3**
(ophthalmic formulations containing chelates and enhancers for prevention and treatment of eye disorders)

L3 ANSWER 12 OF 51 USPATFULL on STN

AB The present invention relates to compositions and methods for inhibiting and reversing nonenzymatic cross-linking (protein aging). Accordingly, compositions are disclosed which comprise an agent capable of inhibiting the formation of advanced glycosylation endproducts of target proteins,

and which additionally reverse pre-formed crosslinks in the advanced glycosylation endproducts by cleaving alpha-dicarbonyl-based protein crosslinks present in the advanced glycosylation endproducts. Certain useful agents are thiazolium salts. The method comprises contacting the target protein with the composition. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A novel immunoassay for detection of the reversal of the nonenzymatic crosslinking is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
2004:45081 Preventing and reversing the formation of advance glycosylation endproducts.
Cerami, Anthony, Shelter Island, NY, UNITED STATES
Ulrich, Peter C., Old Tappan, NJ, UNITED STATES
Wagle, Dilip R., Valley Cottage, NY, UNITED STATES
Hwang, San-Bao, Sudbury, MA, UNITED STATES
Vasan, Sara, Yonkers, NY, UNITED STATES
Egan, John J., Mountain Lakes, NJ, UNITED STATES
US 2004034074 A1 20040219
APPLICATION: US 2003-418398 A1 20030418 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **181069-80-7P**
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

L3 ANSWER 13 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN
AB Background: Increased formation of advanced glycosylation end-products on body proteins is a consequence of aging and leads to exaggerated collagen crosslinking eventually increasing cardiovascular stiffness. This study reports our initial inquires into the cardiovascular and renal effects of a cross-link breaker (ALT-711) in aged spontaneously hypertensive rats (SHR). Methods and results: The first experiment, in 45-wk-old SHR, showed that (among four doses) the dose of 1 mg/kg/d of ALT-711 given for 4 mo was most effective in reducing left ventricular and aortic mass indexes. ALT-711 also reduced left ventricular hydroxyproline concentration (5.8±0.2 v 5.1±0.3 mg/g in controls, P <.05); however, it did not affect systemic or regional hemodynamics. In older SHR, ALT-711 (1 mg/kg/d) reduced (P <.05) systolic pressure (tail-cuff) (from 203±3 mm Hg at outset to 187±3 mm Hg at 8 wk). Systolic pressure remained unchanged in placebo-treated rats. In addition, left ventricular index (3.09±0.10 v 3.44±0.05 mg/g) and aortic mass index (1.54±0.04 v 1.74±0.05 mg/mm) were reduced by ALT-711. In the third experiment, 1-yr-old SHR were given vehicle or ALT-711 (1 mg/kg/d) or placebo until natural death. After 3 mo, ALT-711 markedly reduced urinary protein excretion (74.5±8.6 v 135.4±11.8 mg/24 h). Echocardiog. studies, performed at the outset and after 3 and 6 mo, revealed two changed indexes. Left ventricular end-diastolic diameter increased more in control than in ALT rats, whereas E-wave deceleration time decreased more in control than in ALT rats. Conclusions: Therapy with ALT-711 exerted beneficial cardiovascular and renal effects in aged SHR, improving systolic pressure, left ventricular mass, geometry, and hydroxyproline content while reducing urinary protein excretion.
2004:281528 Document Number 141:360381 Cardiovascular and renal effects of a collagen cross-link breaker (ALT 711) in adult and aged spontaneously hypertensive rats. Susic, Dinko; Varagic, Jasmina; Frohlich, Edward D. (Hypertension Research Laboratory, Ochsner Clinic Foundation, New Orleans,

LA, USA). American Journal of Hypertension, 17(4), 328-333 (English) 2004. CODEN: AJHYE6. ISSN: 0895-7061. Publisher: Elsevier Science Inc..

IT **181069-80-7**, ALT 711
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(collagen cross-linker ALT 711 effectively reduced left ventricular and aortic indexes, left ventricular hydroxy proline content, systolic pressure, proteinuria, left ventricular diastolic diameter, E-wave deceleration in aged SHR)

L3 ANSWER 14 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB A review. Although the features of diabetic cardiomyopathy, atherosclerosis, and nephropathy have been clin. characterized, the pathogenesis and the mechanisms underlying the abnormalities in the diabetic heart and kidney are not fully understood. During the past several years, in an attempt to discover interventions for diabetes-related complications, researchers have refocused their attention from the hemodynamic aspects of the disease to the biochem. interactions of glucose and proteins. Diabetes is a disorder of chronic hyperglycemia, and glucose participates in diabetic complications such as atherosclerosis, cardiac dysfunction, and nephropathy. Chronic hyperglycemia accelerates the reaction between glucose and proteins and leads to the formation of advanced glycation end products (AGE), which form irreversible cross-links with many macromols. such as collagen. In diabetes, these AGE accumulate in tissues at an accelerated rate. The development of the novel compound dimethyl-3-phenacylthiazolium chloride (alagebrium chloride), which chemical breaks AGE cross-links, led to several preclin. animal studies that showed an attenuation or reversal of disease processes of the heart and kidney. In diabetes, AGE not only structurally stiffen structural collagen backbones but also act as agonists to AGE receptors (RAGE) on various cell types, which stimulate the release of profibrotic growth factors, promote collagen deposition, increase inflammation, and ultimately lead to tissue fibrosis. In the heart, large vessels, and kidney, these reactions produce diastolic dysfunction, atherosclerosis, and renal fibrosis. Administration of the cross-link breaker alagebrium chloride in these diabetic animals attenuates these pathol. phenomena, restoring functionality to the heart, vasculature, and kidney.

2004:1089060 Document Number 143:4827 Importance of advanced glycation end products in diabetes-associated cardiovascular and renal disease. Cooper, Mark E. (Danielle Alberti Centre for Diabetic Complications, Wynn Domain, Vascular Division, Baker Heart Research Institute, Melbourne, Australia). American Journal of Hypertension, 17(12, Pt. 2), 31S-38S (English) 2004. CODEN: AJHYE6. ISSN: 0895-7061. Publisher: Elsevier Inc..

IT **341028-37-3**, Alagebrium chloride
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alagebrium chloride break AGE receptor agonist AGE cross links in chronic hyperglycemia, attenuates pathol. phenomena, restoring functionality of heart, vasculature and kidney in rat and mouse model)

L3 ANSWER 15 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB A review. Advanced glycation end product (AGE) formation that occurs with aging and diabetes leads to the crosslinking of proteins and subsequent changes in the physicochem. properties of tissues. Cellular responses to AGE that lead to either pathol. conditions or removal of AGE are mediated by a number of receptors that have been identified on various cell types such

as macrophages, endothelial cells, and smooth-muscle cells. Mechanisms by which AGE affect the cardiovascular system include AGE crosslinking of long-lived proteins such as collagen and elastin and altered cellular responses. Alagebrium (3-phenacyl-4,5-dimethylthiazolium chloride, ALT-711) is the first drug in a new class of thiazolium therapeutic agents that break established AGE cross-links between proteins. In animal studies, alagebrium was effective in reducing large artery stiffness, slowing pulse-wave velocity, enhancing cardiac output, and improving left ventricular diastolic distensibility. In human studies to determine safety and efficacy, alagebrium was safe and well tolerated. In the first phase 2 clin. study, alagebrium improved arterial compliance in elderly patients with vascular stiffening. In two subsequent phase 2 clin. studies, one addressing diastolic heart failure and the other addressing systolic hypertension, alagebrium was effective in improving cardiac function and uncontrolled systolic blood pressure, particularly in more severely affected patients. Addnl. clin. studies to determine the utility of alagebrium in treating cardiovascular disorders associated with aging are in progress.

2004:1089059 Document Number 143:4826 Advanced glycation end-product cross-link breakers: A novel approach to cardiovascular pathologies related to the aging process. Bakris, George L.; Bank, Alan J.; Kass, David A.; Neutel, Joel M.; Preston, Richard A.; Oparil, Suzanne (Rush University Medical Center, Chicago, IL, USA). American Journal of Hypertension, 17(12, Pt. 2), 23S-30S (English) 2004. CODEN: AJHYE6. ISSN: 0895-7061. Publisher: Elsevier Inc..

IT **341028-37-3**, ALT-711
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phase 2 clin. study of ALT-711 which break AGE cross-link between protein was effective, well tolerated in improving cardiac function by controlling systolic blood pressure, vascular stiffening, hypertension in elderly patient)

L3 ANSWER 16 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB The invention relates to the discovery that 3-deoxyglucosone (3DG) and other alpha-dicarbonyl sugars associated diseases and disorders are present and produced in the skin. Further, the invention relates to the discovery that amadorase, an enzyme that mediates 3DG synthesis, is also present in the skin. Thus, the invention further relates to methods of inhibiting production and function of 3-deoxyglucosone and other alphadicarbonyl sugars in skin thereby treating or prevention various diseases, disorders or conditions. Addnl., the invention relates to treatment of various diseases, disorders or conditions associated with or mediated by oxidative stress since 3DG induces ROS and AGEs, which are associated with the inflammatory response caused by oxidative stress.

2003:856039 Document Number 139:369668 Inhibition of 3-deoxyglucosone and α-dicarbonyl sugars in skin and therapeutic uses for oxidative stress related diseases. Tobia, Annette; Kappler, Francis (Dynamis Therapeutics, Inc., USA). PCT Int. Appl. WO 2003089601 A2 20031030, 192 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US12003 20030417. PRIORITY: US 2002-2002/PV37310U 20020417; US 2002-2002/PV39253U

20020627; US 2002-2002/198706 20020718.
IT **181069-80-7**
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of 3-deoxyglucosone and α-dicarbonyl sugars in skin and therapeutic uses for oxidative stress related diseases)

L3 ANSWER 17 OF 51 USPATFULL on STN
AB The invention relates to a method of removing 3-deoxyglucosone and other alpha-dicarbonyl sugars from skin. The invention further relates to methods of inhibiting production and function of 3-deoxyglucosone and other alpha-dicarbonyl sugars in skin. The invention also relates to methods of treating 3-deoxyglucosone and other alpha-dicarbonyl sugars associated diseases and disorders of skin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
2003:311845 3-deoxyglucosone and skin.
Tobia, Annette, Wyndmoor, PA, UNITED STATES
Kappler, Francis, Philadelphia, PA, UNITED STATES
US 2003219440 A1 20031127
APPLICATION: US 2002-198706 A1 20020718 (10)
PRIORITY: US 2002-392530P 20020627 (60)
US 2002-373103P 20020417 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **181069-80-7**
(inhibition of 3-deoxyglucosone and α-dicarbonyl sugars in skin and therapeutic uses for oxidative stress related diseases)

L3 ANSWER 18 OF 51 USPATFULL on STN
AB A method and composition for the treatment of hair, nail, ex-vivo organ, ex-vivo cell or ex-vivo tissue to improve the biomechanical and diffusional characteristics comprising an effective amount of a compound selected from the group consisting of compounds of the formula (I):
##STR1##

or the formula (II):

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
2003:264762 Method and composition for rejuvenating hair, nails, tissues, cells and organs by ex-vivo or immersive treatment.
Brines, Michael L., Woodbridge, CT, UNITED STATES
Cerami, Anthony, Croton-On-Hudson, NY, UNITED STATES
US 2003185776 A1 20031002
APPLICATION: US 2003-392450 A1 20030318 (10)
PRIORITY: US 2001-263300P 20010122 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **341028-37-3**
(compns. containing thiazolium compound for rejuvenating hair and nails and tissues and cells and organs)

L3 ANSWER 19 OF 51 USPATFULL on STN
AB The present invention relates to compositions and methods for inhibiting and reversing nonenzymatic cross-linking (protein aging). Accordingly, a composition is disclosed which comprises a thiazolium compound capable of inhibiting, and to some extent reversing, the formation of advanced

glycosylation endproducts of target proteins by reacting with the carbonyl moiety of the early glycosylation product of such target proteins formed by their initial glycosylation. The method comprises contacting the target protein with the composition. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A novel immunoassay for detection of the reversal of the nonenzymatic crosslinking is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
2003:308308 Preventing and reversing advanced glycosylation endproducts.
Cerami, Anthony, Shelter Island, NY, United States
Ulrich, Peter C., Old Tappan, NJ, United States
Wagle, Dilip R., Valley Cottage, NY, United States
Hwang, San-Bao, Sudbury, MA, United States
Vasan, Sara, Yonkers, NY, United States
Egan, John J., New York City, NY, United States
Alteon Inc., Ramsey, NJ, United States (U.S. corporation)
US 38330 E1 20031125
US 5656261 19970812 (Original)
APPLICATION: US 1999-373345 19990812 (9)
US 1995-375155 19950118 (Original)
DOCUMENT TYPE: Reissue; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **181069-80-7P**
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

L3 ANSWER 20 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN
AB Aging and diabetes mellitus (DM) both affect the structure and function of the myocardium, resulting in increased collagen in the heart and reduced cardiac function. As part of this process, hyperglycemia is a stimulus for the production of advanced glycation end products (AGEs), which covalently modify proteins and impair cell function. The goals of this study were first to examine the combined effects of aging and DM on hemodynamics and collagen types in the myocardium in 12 dogs, 9-12 yr old, and second to examine the effects of the AGE crosslink breaker phenyl-4,5-dimethylthazolium chloride (ALT-711) on myocardial collagen protein content, aortic stiffness, and left ventricular (LV) function in the aged diabetic heart. The alloxan model of DM was utilized to study the effects of DM on the aging heart. DM induced in the aging heart decreased LV systolic function (LV ejection fraction fell by 25%), increased aortic stiffness, and increased collagen type I and type III protein content. ALT-711 restored LV ejection fraction, reduced aortic stiffness and LV mass with no reduction in blood glucose level (199±17 mg/dL), and reversed the upregulation of collagen type I and type III. Myocardial LV collagen solubility (%) increased significantly after treatment with ALT-711. These data suggest that an AGE crosslink breaker may have a therapeutic role in aged patients with DM.
2004:1425 Document Number 140:91894 Glycation end-product cross-link breaker reduces collagen and improves cardiac function in aging diabetic heart. Liu, Jing; Masurekar, Malthi R.; Vatner, Dorothy E.; Jyothirmayi, Garikiparthy N.; Regan, Timothy J.; Vatner, Stephen F.; Meggs, Leonard G.; Malhotra, Ashwani (Department of Cell Biology and Molecular Medicine, University of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, NJ, 07101, USA). American Journal of Physiology, 285(6, Pt. 2), H2587-H2591 (English) 2003. CODEN: AJPHAP. ISSN: 0002-9513.

Publisher: American Physiological Society.

IT **341028-37-3**, ALT-711
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glycation end-product crosslink breaker reduces collagen and improves cardiac function in aging diabetic heart)

L3 ANSWER 21 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB Renal accumulation of advanced glycation end products (AGEs) has been linked to the progression of diabetic nephropathy. Cleavage of pre-formed AGEs within the kidney by a cross-link breaker, such as ALT-711, may confer renoprotection in diabetes. STZ diabetic rats were randomized into (a) no treatment (D); (b) treatment with the AGE cross-link breaker, ALT-711, weeks 16-32 (DALT early); and (c) ALT-711, weeks 24-32 (DALT late). Treatment with ALT-711 resulted in a significant reduction in diabetes-induced serum and renal AGE peptide fluorescence, associated with decreases in renal carboxymethyllysine and RAGE immunostaining. Crosslinking of tail tendon collagen seen in diabetic groups was attenuated only by 16 wk of ALT-711 treatment. ALT-711, independent of treatment duration, retarded albumin excretion rate (AER), reduced blood pressure, and renal hypertrophy. It also reduced diabetes-induced increases in gene expression of transforming growth factor β1 (TGF-β1), connective tissue growth factor (CTGF), and collagen IV. However, glomerulosclerotic index, tubulointerstitial area, total renal collagen, nitrotyrosine, protein expression of collagen IV, and TGF-β1 only showed improvement with early ALT treatment alone. This study demonstrates the utility of a cross-link breaker as a treatment for diabetic nephropathy and describes effects not only on renal AGEs but on putative mediators of renal injury, such as prosclerotic cytokines and oxidative stress.

2003:730751 Document Number 139:301751 The breakdown of pre-existing advanced glycation end products is associated with reduced renal fibrosis in experimental diabetes. Forbes, Josephine M.; Thallas, Vicki; Thomas, Merlin C.; Founds, Hank W.; Burns, Wendy C.; Jerums, George; Cooper, Mark E. (Division of Diabetic Complications, Baker Medical Research Institute, Melbourne, 8008, Australia). FASEB Journal, 17(12), 1762-1764, 10.1096/fj.02-1102fje (English) 2003. CODEN: FAJOEC. ISSN: 0892-6638. Publisher: Federation of American Societies for Experimental Biology.

IT **341028-37-3**, ALT 711
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT 711; breakdown of pre-existing advanced glycation end products is associated with reduced renal fibrosis in exptl. diabetes)

L3 ANSWER 22 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB The formation of advanced glycation end products (AGEs) on extracellular matrix components leads to accelerated increases in collagen cross linking that contributes to myocardial stiffness in diabetes. This study determined the effect of the crosslink breaker, ALT-711 on diabetes-induced cardiac disease. Streptozotocin diabetes was induced in Sprague-Dawley rats for 32 wk. Treatment with ALT-711 (10 mg/kg) was initiated at week 16. Diabetic hearts were characterized by increased left ventricular (LV) mass and brain natriuretic peptide (BNP) expression, decreased LV collagen solubility, and increased collagen III gene and protein expression. Diabetic hearts had significant increases in AGEs and increased expression of the AGE receptors, RAGE and AGE-R3, in association with increases in gene and protein expression of connective tissue growth factor (CTGF). ALT-711

treatment restored LV collagen solubility and cardiac BNP in association with reduced cardiac AGE levels and abrogated the increase in RAGE, AGE-R3, CTGF, and collagen III expression. The present study suggests that AGEs play a central role in many of the alterations observed in the diabetic heart and that cleavage of preformed AGE crosslinks with ALT-711 leads to attenuation of diabetes-associated cardiac abnormalities in rats. This provides a potential new therapeutic approach for cardiovascular disease in human diabetes.

2003:274376 Document Number 139:207499 A Breaker of Advanced Glycation End Products Attenuates Diabetes-Induced Myocardial Structural Changes. Candido, Riccardo; Forbes, Josephine M.; Thomas, Merlin C.; Thallas, Vicki; Dean, Rachael G.; Burns, Wendy C.; Tikellis, Christos; Ritchie, Rebecca H.; Twigg, Stephen M.; Cooper, Mark E.; Burrell, Louise M. (Division of Diabetes, Lipoproteins, and Metabolism, Baker Heart Research Institute, Victoria, Australia). Circulation Research, 92(7), 785-792 (English) 2003. CODEN: CIRUAL. ISSN: 0009-7330. Publisher: Lippincott Williams & Wilkins.

IT **341028-37-3**, ALT 711
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT-711 inhibition of AGE crosslinking attenuates diabetes-induced myocardial structural changes)

L3 ANSWER 23 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB A review. Long-lived structural proteins, collagen and elastin, undergo continual non-enzymic crosslinking during aging and in diabetic individuals. This abnormal protein crosslinking is mediated by advanced glycation end products (AGEs) generated by non-enzymic glycosylation of proteins by glucose. The AGE-derived protein crosslinking of structural proteins contributes to the complications of long-term diabetes such as nephropathy, retinopathy, and neuropathy. AGE-crosslinks have also been implicated in age-related cardiovascular diseases. Potential treatment strategies for these AGE-derived complications include prevention of AGE-formation and breaking of the existing AGE-crosslinks. The therapeutic potential of the AGE-inhibitor, pimagedine (aminoguanidine), has been extensively investigated in animal models and in Phase 3 clin. trials. This review presents the pre-clin. and clin. studies using ALT-711, a highly potent AGE-crosslink breaker that has the ability to reverse already-formed AGE-crosslinks. Oral administration of ALT-711 has resulted in a rapid improvement in the elasticity of stiffened myocardium in exptl. animals. Topical administration of ALT-711 was effective in improving the skin hydration of aged rats. The therapeutic potential of crosslink breakers for cardiovascular complications and dermatol. alterations associated with aging and diabetes is discussed.

2003:804088 Document Number 140:121913 Therapeutic potential of breakers of advanced glycation end product-protein crosslinks. Vasan, Sara; Foiles, Peter; Founds, Hank (Alteon Inc., Ramsey, NJ, 07446, USA). Archives of Biochemistry and Biophysics, 419(1), 89-96 (English) 2003. CODEN: ABBIA4. ISSN: 0003-9861. Publisher: Elsevier Science.

IT **341028-37-3**, ALT 711
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT 711; therapeutic potential of AGE crosslink breakers)

L3 ANSWER 24 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB The purpose of this study was to investigate the effect of N-phenacyl-4,5-dimethylthiazolium bromide (DMPTB), an advanced glycation

end product (AGE) cross-link breaker, on lens protein cross-links formed in vitro and in vivo. DMPTB was synthesized and its structure confirmed by its NMR spectrum. To show whether DMPTB can inhibit AGE crosslinking, recombinant human αA-crystallin was glycated with glucose-6-phosphate (G6P) in the presence and absence of DMPTB. Reversal of the already formed cross-links was studied by treating pre-glycated αA-crystallin with DMPTB. The ability of DMPTB to cleave in vivo formed cross-links was ascertained by treating water-insol. protein fractions from diabetic human lenses with this compound Glycation of αA-crystallin with G6P showed several high mol. weight (HMW) protein bands on the SDS-PAGE gel; DMPTB inhibited the formation of these HMW proteins. Mol. sieve HPLC confirmed the inhibition of formation of larger aggregates not separated by SDS-PAGE. Treatment of pre-glycated αA-crystallin with DMPTB gave evidence for the degradation of the already formed cross--linked HMW aggregates. Both mol. sieve HPLC and reverse-phase HPLC of the water-insol. protein fractions from two diabetic human lenses showed that DMPTB could degrade a major portion of the cross-linked HMW aggregates to lower mol. weight proteins. This suggests that the cross-linked proteins in human lenses are formed predominantly by the advanced glycation process and cross-link breakers like DMPTB may have application for the intervention of protein crosslinking in the eye lens.

2002:958056 Document Number 139:127787 Cleavage of in vitro and in vivo formed lens protein cross-links by a novel cross-link breaker. Hollenbach, Seth; Thampi, Prajitha; Viswanathan, Tito; Abraham, Edathara C. (Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock, AR, 72205, USA). Molecular and Cellular Biochemistry, 243(1&2), 73-80 (English) 2003. CODEN: MCBIB8. ISSN: 0300-8177. Publisher: Kluwer Academic Publishers.

IT **181069-80-7P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(cleavage of lens protein cross-links by a novel cross-link breaker, N-phenacyl-4,5-dimethylthiazolium bromide, in vitro and in aged, diabetic human lenses)

L3 ANSWER 25 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB Advanced glycation end products (AGE), formed by nonenzymic Maillard reactions between carbohydrate and protein, contribute to the increase in chemical modification and crosslinking of tissue proteins with age. Acceleration of AGE formation in collagen during hyperglycemia, with resultant effects on vascular elasticity and basement membrane permeability, is implicated in the pathogenesis of diabetic complications. AGE-breakers, such as N-phenacylthiazolium (PTB) and N-phenacyl-4,5-dimethylthiazolium (PMT) halides, have been proposed as therapeutic agents for reversing the increase in protein crosslinking in aging and diabetes. We have confirmed that these compds., as well as the AGE-inhibitor pyridoxamine (PM), cleave the model AGE crosslink, phenylpropanedione, and have studied the effects of these compds. in reversing the increased crosslinking of skin and tail collagen isolated from diabetic rats. Crosslinking of skin collagen, measured as the half-time for solubilization of collagen by pepsin in 0.5 M acetic acid, was increased .apprx.5-fold in diabetic, compared to nondiabetic rats. Crosslinking of tail tendon collagen, measured as insoly. in 0.05 N acetic acid, was increased .apprx.10-fold. Collagen prepns. were incubated in the presence or absence of AGE-breakers or PM in phosphate buffer, pH 7.4, for 24 h at 37°C. These treatments did not decrease the half-time for

solubilization of diabetic skin collagen by pepsin or increase the acid solubility of diabetic tail tendon collagen. We conclude that, although AGE-breakers and PM cleave model crosslinks, they do not significantly cleave AGE crosslinks formed in vivo in skin collagen of diabetic rats.

2003:212250 Document Number 139:127795 AGE-breakers cleave model compounds, but do not break Maillard crosslinks in skin and tail collagen from diabetic rats. Yang, Shengzu; Litchfield, John E.; Baynes, John W. (Graduate Science Research Center, Department of Chemistry and Biochemistry, University of South Carolina, Columbia, SC, 29208, USA). Archives of Biochemistry and Biophysics, 412(1), 42-46 (English) 2003. CODEN: ABBIA4. ISSN: 0003-9861. Publisher: Elsevier Science.

IT **181069-80-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AGE-breakers cleave model compds., but do not break Maillard crosslinks in skin and tail collagen from diabetic rats)

L3 ANSWER 26 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB A review. The role of advanced glycation end products (AGES) in diabetic nephropathy has been developed during several years of research and increasingly complex AGE biochem. However, the structural diversity of AGE chemical has created new challenges in the search for AGE-based inhibition therapies. The challenges include the need to standardize measurements of serum and tissue AGE levels, identifying nephrotoxic AGE compds., understanding the cell biol. state of AGES in the diabetic kidney, determining the mechanism of action of selective inhibition of the glycation cascade, and forming complementary therapies. Current challenges in the development of new therapies for AGE nephrotoxicity are reviewed.

2003:252556 Document Number 139:332007 New therapies for advanced glycation end product nephrotoxicity: current challenges. Williams, Mark E. (Joslin Diabetes Center and Harvard Medical School, Boston, MA, USA). American Journal of Kidney Diseases, 41(3, Suppl. 1), S42-S47 (English) 2003. CODEN: AJKDDP. ISSN: 0272-6386. Publisher: W. B. Saunders Co..

IT **181069-80-7**, ALT 711
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT 711; new therapies for advanced glycation end product nephrotoxicity)

L3 ANSWER 27 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1

AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the composition to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepared from Glu(OBut)NCA and cephalexin hydrochloride.

2002:556104 Document Number 137:109489 Compositions comprising a polypeptide and an active agent. Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randal J. (USA). U.S. Pat. Appl. Publ. US 2002099013 A1 20020725, 34 pp. (English). CODEN: USXXCO. APPLICATION: US 2001-933708 20010822. PRIORITY: US 2000-2000/PV247928; 20001114; US 2000-2000/PV247621; 20001114; US 2000-2000/PV247620; 20001114; US 2000-2000/PV247595; 20001114; US 2000-2000/PV247594; 20001114; US 2000-2000/PV247635; 20001114; US 2000-2000/PV247634; 20001114; US 2000-2000/PV247606; 20001114; US 2000-2000/PV247607; 20001114; US 2000-2000/PV247608;

20001114; US 2000-2000/PV247609; 20001114; US 2000-2000/PV247610; 20001114; US 2000-2000/PV247611; 20001114; US 2000-2000/PV247702; 20001114; US 2000-2000/PV247701; 20001114; US 2000-2000/PV247700; 20001114; US 2000-2000/PV247699; 20001114; US 2000-2000/PV247698; 20001114; US 2000-2000/PV247807; 20001114; US 2000-2000/PV247833; 20001114.

IT **181069-80-7**, ALT 711
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

L3 ANSWER 28 OF 51 USPATFULL on STN DUPLICATE 2

AB In one embodiment, the present invention relates to compounds and compositions including pharmaceutical compositions containing the compounds and associated methods that uncouple sugar-mediated coupling of proteins, lipids, nucleic acids, and other biomaterials, and any combination thereof. In another embodiment, the compositions and associated methods have utility in vivo to reduce the deleterious effects of sugar-mediated coupling processes in an organism, when the organism is exposed to the compound or composition internally, by ingestion, transdermal application, or other means. In yet another embodiment, the compositions and associated methods are useful for the ex-vivo treatment of organs, cells and tissues and external treatment of hair, nails and skin to rejuvenate them by changing deformability and increase the tissue diffusion coefficient. In a further embodiment, the present invention relates to novel compounds and pharmaceutical compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

2002:330330 Method and composition for rejuvinating cells, tissues organs, hair and nails.
Ulrich, Peter C., Portland, OR, UNITED STATES
Fang, Sheng Ding, Mount Kisco, NY, UNITED STATES
Brines, Michael L., Woodbridge, CT, UNITED STATES
Xie, Qiao-Wen, Yonkers, NY, UNITED STATES
Cerami, Anthony, Sleepy Hollow, NY, UNITED STATES
US 2002188015 A1 20021212
APPLICATION: US 2002-72712 A1 20020207 (10)
PRIORITY: US 2001-267226P 20010207 (60)
DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **341028-37-3**
(preparation of azoles, azines and salts thereof for rejuvenating cells, tissues, organs, hair and nails)

L3 ANSWER 29 OF 51 USPATFULL on STN DUPLICATE 3

AB A method and composition for the treatment of hair, nail, ex-vivo organ, ex-vivo cell or ex-vivo tissue to improve the biomechanical and diffusional characteristics comprising an effective amount of a compound selected from the group consisting of compounds of the formula ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

2002:322004 Method and composition for rejuvenating hair, nails, tissues, cells and organs by ex-vivo or immersive treatment.
Brines, Michael L., Woodbridge, CT, UNITED STATES
Cerami, Anthony, Sleepy Hollow, NY, UNITED STATES
US 2002182165 A1 20021205

APPLICATION: US 2002-55252 A1 20020122 (10)
PRIORITY: US 2001-263300P 20010122 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **341028-37-3**
(compns. containing thiazolium compound for rejuvenating hair and nails and tissues and cells and organs)

L3 ANSWER 30 OF 51 USPATFULL on STN DUPLICATE 4
AB Provided is a method of synthesizing a compound of formula I, ##STR1##

comprising:

(a) reacting a compound of formula II ##STR2##

wherein R.sub.1 and R.sub.2 are independently hydrogen, hydroxy(C.sub.1-C.sub.2)alkyl, or (C.sub.1-C.sub.2)alkyl with,

a compound of formula III ##STR3##

wherein

R.sub.3, R.sub.4, and R.sub.5 are each independently of each other hydrogen, (C.sub.1-C.sub.3)alkyl, (C.sub.1-C.sub.3)alkoxy, or halogen; and

X is a leaving group,

in a solvent having a dielectric constant at 20° C. of at least 30 but no more than 40; and

(b) obtaining the compound I.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
2002:22635 Synthesis of thiazolium compounds.
Wagle, Dilip, New York, NY, UNITED STATES
US 2002013471 A1 20020131
APPLICATION: US 2001-821846 A1 20010329 (9)
PRIORITY: US 2000-192867P 20000329 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **341028-37-3P**
(preparation of)

L3 ANSWER 31 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN
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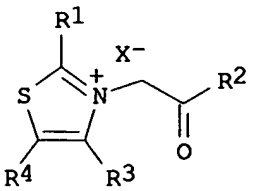

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DELACROIX

AB A composition for the treatment of hair, nail, ex-vivo organ, ex-vivo cell or ex-vivo tissue to improve the biomech. and diffusional characteristics comprising an effective amount of title compds., e.g. [I; R1 = alkyl, CHR5OH, CHR5O2CR6; R5 = alkyl; R6 = alkyl, Ph, halophenyl, alkoxyphenyl, naphthyl; R2 = OH, Ph, halophenyl, alkoxyphenyl, (aromatic) heterocyclyl; R3, R4 = H, alkyl, hydroxyalkyl, Ph; R3R4 = atoms to form an (aromatic) (substituted) ring; X = halide, other pharmaceutically acceptable anion]. Thus, 2-aminopyrimidine in CH2Cl2 was treated dropwise with O-mesitylenesulfonylhydroxylamine in CH2Cl2 at 4° followed by stirring overnight to give 2,3-diaminopyrimidinium mesitylene-2-sulfonate salt. The latter at 10 nM gave 52% reversal of sugar-mediated coupling of albumen to collagen after 2 days.

2002:615361 Document Number 137:169535 Preparation of azoles, azines and salts thereof for rejuvenating cells, tissues, organs, hair and nails.. Ulrich, Peter C.; Fang, Sheng Ding; Brines, Michael; Xie, Qiao Wen; Cerami, Anthony (Farrington Pharmaceuticals, LLC, USA). PCT Int. Appl. WO 2002062301 A2 20020815, 99 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US3714 20020207. PRIORITY: US 2001-2001/PV267226 20010207.

IT **341028-37-3**
RL: COS (Cosmetic use); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of azoles, azines and salts thereof for rejuvenating cells, tissues, organs, hair and nails)

L3 ANSWER 32 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB A composition for the treatment of hair, nail, ex-vivo organ, ex-vivo cell or ex-vivo tissue to improve the biomech. and diffusional characteristics comprises a thiazolium compound Thus, a shampoo contained 30% sodium lauryl sulfate 40.00, lauric diethanolamide 4.00, 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride 1.10, perfume 0.25, Dowicil-200 0.20 and soft water 54.45% by weight

2002:555309 Document Number 137:114210 Compositions containing thiazolium compound for rejuvenating hair, nails, tissues, cells and organs. Brines, Michael L.; Cerami, Anthony (Farrington Pharmaceuticals, LLC, USA). PCT Int. Appl. WO 2002056836 A2 20020725, 40 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US1860 20020122. PRIORITY: US 2001-2001/PV263300 20010122.

IT **341028-37-3**
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. containing thiazolium compound for rejuvenating hair and nails and

tissues and cells and organs)

L3 ANSWER 33 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN
AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the composition to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepared from Glu(OBut)NCA and cephalexin hydrochloride.
2002:332011 Document Number 136:355482 Compositions comprising a polypeptide and an active agent. Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randall J. (New River Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2002034237 A1 20020502, 98 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US26142 20010822. PRIORITY: US 2000-2000/642820 20000822.
IT **181069-80-7**, ALT 711
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

L3 ANSWER 34 OF 51 USPATFULL on STN
AB The present invention relates to compositions and methods for inhibiting and reversing nonenzymatic cross-linking (protein aging). Accordingly, compositions are disclosed which comprise an agent capable of inhibiting the formation of advanced glycosylation endproducts of target proteins, and which additionally reverse pre-formed crosslinks in the advanced glycosylation endproducts by cleaving alpha-dicarbonyl-based protein crosslinks present in the advanced glycosylation endproducts. Certain agents useful are thiazolium salts. The method comprises contacting the target protein with the composition. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A novel immunoassay for detection of the reversal of the nonenzymatic crosslinking is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
2002:337482 Method of treating certain indications associated with hyperglycemia.
Cerami, Anthony, Shelter Island, NY, UNITED STATES
Ulrich, Peter C., Old Tappan, NJ, UNITED STATES
Wagle, Dilip R., Valley Cottage, NY, UNITED STATES
Hwang, San-Bao, Sudbury, MA, UNITED STATES
Vasan, Sara, Yonkers, NY, UNITED STATES
Egan, John J., Mountain Lakes, NJ, UNITED STATES
US 2002192842 A1 20021219
APPLICATION: US 2002-174883 A1 20020619 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **181069-80-7P**
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

L3 ANSWER 35 OF 51 USPATFULL on STN

AB The present invention relates to compositions and methods for inhibiting and reversing nonenzymatic cross-linking (protein aging). Accordingly, compositions are disclosed which comprise an agent capable of inhibiting the formation of advanced glycosylation endproducts of target proteins, and which additionally reverse pre-formed crosslinks in the advanced glycosylation endproducts by cleaving alpha-dicarbonyl-based protein crosslinks present in the advanced glycosylation endproducts. Certain agents useful are thiazolium salts. The method comprises contacting the target protein with the composition. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A immunoassay for detection of the reversal of the nonenzymatic crosslinking is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

2002:217094 Method of treating certain indications associated with hyperglycemia.
Cerami, Anthony, Shelter Island, NY, United States
Ulrich, Peter C., Old Tappan, NJ, United States
Wagle, Dilip R., Valley Cottage, NY, United States
Hwang, San-Bao, Sudbury, MA, United States
Vasan, Sara, Yonkers, NY, United States
Egan, John J., Mountain Lakes, NJ, United States
Alteon. Inc., Ramsey, NJ, United States (U.S. corporation)The Picower Institute for Medical Research, Manhasset, NY, United States (U.S. corporation)
US 6440749 B1 20020827
APPLICATION: US 1999-470482 19991222 (9)
DOCUMENT TYPE: Utility; GRANTED.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **181069-80-7P**
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

L3 ANSWER 36 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB Background: Crosslinking of macromols. like collagen plays an important role in the development of complications in diabetes and ageing. One of the underlying mechanisms of this crosslinking is the formation of advanced glycation endproducts (AGEs). Methods: In this study, we assessed the use of differential scanning calorimetry (DSC) for the determination of these cross-links and the effects of an AGE inhibitor and breaker. Results: Treatment with N-phenacylthiazolium bromide (ALT-711) of diabetic rats with 2 mo duration of diabetes normalized large artery stiffness, assessed by characteristic input impedance and systemic arterial compliance, but with the use of DSC, no statistical difference in crosslinking between control and treated animals could be measured. In addition, we performed in vitro incubation of collagen prepns. with ribose and glucose to assess the DSC method as well as the influence of AGE breakers and inhibitors. Incubation of rat tail tendon (RTT) with 100 mmol/l glucose showed an increase in collagen crosslinking expressed as an increase in shrinkage temperature (Ts). Addition of aminoguanidine (AG), an inhibitor of AGE formation, prior to glucose incubation showed a slower increase of the amount of glucose-derived crosslinking. Replacing glucose with ribose showed a quicker increase in crosslinking and less effect on crosslinking by adding aminoguanidine, demonstrating the higher reactivity

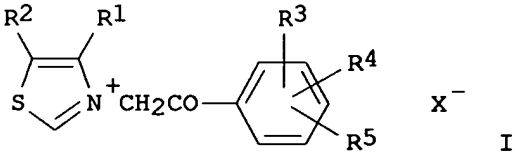
of pentoses above hexoses. Similar expts. with rat skin samples (RSS) showed that RSS (type III collagen) are less susceptible to glucose-mediated crosslinking than RTT (type I collagen). We observed no effect of addition of ALT-711, a breaker of glucose-derived cross-links, on the extent of collagen crosslinking in both RTT and RSS. Conclusion: Overall, DSC is considered a useful method for assessing glucose-mediated crosslinking in vitro with nonphysiol. glucose concns. The in vivo use in biol. samples is limited due to the lack of sensitivity. However, DSC remains a quick and well-quantitated method in comparison with other methods, like enzymic digestibility.

2002:380419 Document Number 137:137181 Glucose-mediated cross-linking of collagen in rat tendon and skin. Mentink, Cyriel J. A. L.; Hendriks, Marc; Levels, Anita A. G.; Wolffenbuttel, Bruce H. R. (Department of Endocrinology, Maastricht University Hospital, Maastricht, 6202 AZ, Neth.). Clinica Chimica Acta, 321(1-2), 69-76 (English) 2002. CODEN: CCATAR. ISSN: 0009-8981. Publisher: Elsevier Science Ltd..

IT **181069-80-7**, ALT-711
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glucose-mediated crosslinking of collagen in rat tendon and skin)

L3 ANSWER 37 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

GI



I

AB Title compds. I (R1, R2 = H, alkyl, hydroxyalkyl; R3, R4, R5 = H, alkyl, alkoxy, halo; X is a leaving group) were prepared by reaction of thiazoles with R3R4R5C6H2COCH2X in solvents having a dielec. constant at 20° of 30-40. Thus, 9.52 kg of 4,5-dimethylthiazole and 13.00 kg of 2-chloroacetophenone were refluxed in MeCN under N for 96.5 h to give 17.99 kg of 4,5-dimethyl-3-(2-oxo-2-phenylethyl)thiazolium chloride, which was subjected to a purification process.

2001:730717 Document Number 135:272952 Synthesis of thiazolium compounds. Wagle, Dilip (Alteon, Inc., USA). PCT Int. Appl. WO 2001072724 A1 20011004, 16 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US10355 20010329. PRIORITY: US 2000-PV192867 20000329.

IT **341028-37-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

L3 ANSWER 38 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB The advanced glycation end-product (AGE) hypothesis proposes that

accelerated chemical modification of proteins by glucose during hyperglycemia contributes to the pathogenesis of diabetic complications. The two most commonly measured AGEs, Nε-(carboxymethyl)lysine and pentosidine, are glycoxidn. products, formed from glucose by sequential glycation and autoxidn. reactions. Although several compds. have been developed as AGE inhibitors and are being tested in animal models of diabetes and in clin. trials, the mechanism of action of these inhibitors is poorly understood. In general, they are thought to function as nucleophilic traps for reactive carbonyl intermediates in the formation of AGEs; however alternative mechanisms of actions, such as chelation, have not been rigorously examined To distinguish between the carbonyl trapping and antioxidant activity of AGE inhibitors, we have measured the chelating activity of the inhibitors by determining the concentration required for 50% inhibition
of the rate of copper-catalyzed autoxidn. of ascorbic acid in phosphate buffer. All AGE inhibitors studied were chelators of copper, as measured by inhibition of metal-catalyzed autoxidn. of ascorbate. Apparent binding consts. for copper ranged from ~2 mM for aminoguanidine and pyridoxamine, to 10-100 μM for carnosine, phenazinediamine, OPB-9195 and tenilsetam. The AGE-breakers, phenacylthiazolium and phenacyldimethylthiazolium bromide, and their hydrolysis products, were among the most potent inhibitors of ascorbate oxidation We conclude that, at millimolar concns. of AGE inhibitors used in many in vitro studies, inhibition of AGE formation results primarily from the chelating or antioxidant activity of the AGE inhibitors, rather than their carbonyl trapping activity. Further, at therapeutic concns., the chelating activity of AGE inhibitors and AGE-breakers may contribute to their inhibition of AGE formation and protection against development of diabetic complications.

2002:43332 Document Number 136:288862 Chelating activity of advanced glycation end-product inhibitors. Price, David L.; Rhett, Patricia M.; Thorpe, Suzanne R.; Baynes, John W. (Department of Chemistry and Biochemistry, University of South Carolina, Columbia, SC, 29208, USA). Journal of Biological Chemistry, 276(52), 48967-48972 (English) 2001. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

IT **181069-80-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chelating activity of advanced glycation end-product inhibitors)

L3 ANSWER 39 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB A review. Glucose and other reducing sugars react non-enzymically with proteins leading to the formation of advanced glycosylation end products (AGEs) and AGE-derived protein crosslinking. Formation of AGEs is a normal physiol. process, which is accelerated under the hyperglycemic condition in diabetes. Under normal conditions, AGEs build up slowly and accumulate as one ages. Numerous studies have indicated that AGEs contribute to the pathol. events leading to diabetic complications, such as age-related diseases, including nephropathy, retinopathy, vasculopathy and neuropathy. Potential therapeutic approaches to prevent these complications include pharmacol. inhibition of AGE formation and disruption of pre-formed AGE-protein cross-links. Studies using animal models and preliminary clin. trials have shown the ability of the AGE-inhibitor, pimagedine and the cross-link breaker, ALT-711, to reduce the severity of pathologies of advanced glycosylation. These agents offer potential treatments for glucose-derived complications of diabetes and ageing.

2001:849132 Document Number 136:128484 Therapeutic potential of AGE inhibitors and breakers of AGE protein cross-links. Vasan, Sara; Foiles, Peter G.; Founds, Henry W. (Alteon, Inc., Ramsey, NJ, 07446, USA). Expert Opinion on Investigational Drugs, 10(11), 1977-1987 (English) 2001. CODEN: EOIDER. ISSN: 1354-3784. Publisher: Ashley Publications Ltd..

IT **341028-37-3**, ALT 711
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic potential of AGE inhibitors and breakers of AGE protein cross-links)

L3 ANSWER 40 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB Arterial stiffening with increased pulse pressure is a leading risk factor for cardiovascular disease in the elderly. We tested whether ALT-711, a novel nonenzymic breaker of advanced glycation end-product crosslinks, selectively improves arterial compliance and lowers pulse pressure in older individuals with vascular stiffening. Nine US centers recruited and randomly assigned subjects with resting arterial pulse pressures >60 mm Hg and systolic pressures >140 mm Hg to once-daily ALT-711 (210 mg; n=62) or placebo (n=31) for 56 days. Preexisting antihypertensive treatment (90% of subjects) was continued during the study. Morning upright blood pressure, stroke volume, cardiac output, systemic vascular resistance, total arterial compliance, carotid-femoral pulse wave velocity, and drug tolerability were assessed. ALT-711 netted a greater decline in pulse pressures than placebo (-5.3 vs. -0.6 mm Hg at day 56; P=0.034 for treatment effect by repeated-measures ANOVA). Systolic pressure declined in both groups, but diastolic pressure fell less with ALT-711 (P=0:056). Mean pressure declined similarly in both groups (-4 mm Hg; P<0.01 for each group, P=0.34 for treatment effect). Total arterial compliance rose 15% in ALT-711-treated subjects vs. no change with placebo (P=0.015 vs. ALT-711), an effect that did not depend on reduced mean pressure. Pulse wave velocity declined 8% with ALT-711 (P<0.05 at day 56, P=0.08 for treatment effect). Systemic arterial resistance, cardiac output, and heart rate did not significantly change in either group. ALT-711 improves total arterial compliance in aged humans with vascular stiffening, and it may provide a novel therapeutic approach for this abnormality, which occurs with aging, diabetes, and isolated systolic hypertension.

2001:783968 Document Number 136:112431 Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. Kass, David A.; Shapiro, Edward P.; Kawaguchi, Miho; Capriotti, Anne R.; Scuteri, Angelo; deGroof, Robert C.; Lakatta, Edward G. (Division of Cardiology, The Johns Hopkins Medical Institutions, Baltimore, MD, 21287, USA). Circulation, 104(13), 1464-1470 (English) 2001. CODEN: CIRCAZ. ISSN: 0009-7322. Publisher: Lippincott Williams & Wilkins.

IT **181069-80-7**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT 711; improved arterial compliance by a novel advanced glycation end-product crosslink breaker)

L3 ANSWER 41 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB Nonenzymic glycosylation and crosslinking of proteins by glucose contributes to an age-associated increase in vascular and myocardial stiffness. Some recently synthesized thiazolium compds. selectively break these protein cross-links, reducing collagen stiffness. We investigated the effects of 3-phenacyl-4,5-dimethylthiazolium chloride (ALT-711) on arterial and left ventricular (LV) properties and their coupling in old,

healthy, nondiabetic Macaca mulatta primates (age 21±3.6 yr). Serial measurements of arterial stiffness indexes [i.e., aortic pulse wave velocity (PWV) and augmentation (AGI) of carotid arterial pressure waveform] as well as echocardiog. detns. of LV structure and function were made before and for 39 wk after 11 i.m. injections of ALT-711 at 1.0 mg/kg body weight every other day. Heart rate, brachial blood pressure, and body weight were unchanged by the drug. PWV and AGI decreased to a nadir at 6 wk [PWV to 74.2±4.4% of baseline (B), P = 0.007; AGI to 41±7.3% of B, P = 0.046], and thereafter gradually returned to baseline. Concomitant increases in LV end diastolic diameter to 116.7±2.7% of B, P = 0.02; stroke volume index (SVindex) to 173.1±40.1% of B, P = 0.01; and systolic fractional shortening to 180±29.7% of B, P = 0.01 occurred after drug treatment The LV end systolic pressure/SVindex, an estimate of total LV vascular load, decreased to 60±12.1% of B (P = 0.02). The LV end systolic diameter/SVindex, an estimate of arterio-ventricular coupling, was improved (decreased to 54.3±11% of B, P < 0.002). Thus, in healthy older primates without diabetes, ALT-711 improved both arterial and ventricular function and optimized ventriculo-vascular coupling. This previously unidentified cross-link breaker may be an effective pharmacol. therapy to improve impaired cardiovascular function that occurs in the context of heart failure associated with aging, diabetes, or hypertension, conditions in which arterial and ventricular stiffness are increased.

2001:120548 Document Number 134:290192 A cross-link breaker has sustained effects on arterial and ventricular properties in older rhesus monkeys. Vaitkevicius, Peter V.; Lane, Mark; Spurgeon, Harold; Ingram, Donald K.; Roth, George S.; Egan, John J.; Vasan, Sara; Wagle, Dilip R.; Ulrich, Peter; Brines, Michael; Wuerth, Jean Paul; Cerami, Anthony; Lakatta, Edward G. (Intramural Research Program, Gerontology Research Center, National Institute on Aging, National Institutes of Health, Baltimore, MD, 21224, USA). Proceedings of the National Academy of Sciences of the United States of America, 98(3), 1171-1175 (English) 2001. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

IT **181069-80-7**, ALT-711
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of cross-link breaker on arterial and ventricular properties in aging rhesus monkeys)

L3 ANSWER 42 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB A review with 6 refs. Vascular and/or myocardial stiffness is a major problem in ageing, diabetes, hypertension and heart failure. The development of the stiffness is partly due to the formation of glucose-dependent cross-links in the collagen. ALT-711 cleaves these cross-links. In aged-rhesus monkeys, ALT-711 decreases vascular stiffness and this effect is reversible. ALT-711 also decreases myocardial stiffness in the monkeys but this effect is not reversible in 39 wk. ALT-711 has potential in the treatment of the stiffness associated with diabetes, hypertension and heart failure.

2001:321927 Document Number 135:131603 ALT-711 decreases cardiovascular stiffness and has potential in diabetes, hypertension and heart failure. Doggrell, Sheila A. (Doggrell Biomedical Communications, Auckland, N. Z.). Expert Opinion on Investigational Drugs, 10(5), 981-983 (English) 2001. CODEN: EOIDER. ISSN: 1354-3784. Publisher: Ashley Publications Ltd..

IT **341028-37-3**, ALT 711
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(ALT-711 decreases cardiovascular stiffness and has potential in diabetes, hypertension and heart failure)

L3 ANSWER 43 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN
AB A review. Recent studies have revealed that reducing sugars, such as glucose, react with proteins through non-enzymic glycosylation to form irreversible, covalently crosslinked proteins known as advanced glycation endproducts (AGEs). Furthermore, it has been demonstrated that this naturally occurring process, accelerated in diabetics due to hyperglycemia, impairs biol. functions leading to cardiovascular disorders, as well as diabetic and age-related complications. Pharmaceutical intervention to prevent or reverse these complications have focused on inhibiting the formation of AGEs by compds. such as dimethyl-3-phenacylthiazolium chloride or breaking the glucose derived crosslinks by selective cleavage. Intervention targeted at AGE crosslinks in vivo offers a way to interfere with age-related changes of tissues.
2002:527729 Document Number 138:100199 Pharmaceutical intervention of advanced glycation endproducts. Cerami, Anthony; Ulrich, Peter (The Kenneth S. Warren Laboratories, Tarrytown, NY, 10591, USA). Novartis Foundation Symposium, 235(Aging Vulnerability), 202-216 (English) 2001. CODEN: NFSYF7. ISSN: 1528-2511. Publisher: John Wiley & Sons Ltd..
IT **341028-37-3**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chemical of advanced glycation endproducts formation, role of advanced glycation endproducts in age-related complications and pharmacol. intervention)

L3 ANSWER 44 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN
AB On page 2809, paragraph 1, line 23, the name of the cross-link breaker should be 4,5-dimethyl-3-(2-oxo-2-phenylethyl)-thiazolium chloride instead of phenyl-4,5-dimethylthazolium chloride.
2000:341544 Document Number 134:51229 An advanced glycation end-product cross-link breaker can reverse age-related increases in myocardial stiffness. [Erratum to document cited in CA132:329694]. Asif, Mohammad; Egan, John; Vasan, Sara; Jyothirmayi, Garikiparthy N.; Masurekar, Malthi R.; Lopez, Santos; Williams, Chandra; Torres, Ramon L.; Wagle, Dilip; Ulrich, Peter; Cerami, Anthony; Brines, Michael; Regan, Timothy J. (New Jersey Medical School, University Medicine and Dentistry New Jersey, Newark, NJ, 07103, USA). Proceedings of the National Academy of Sciences of the United States of America, 97(10), 5679 (English) 2000. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.
IT **181069-80-7**, ALT 711
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(an advanced glycation endproduct cross-link breaker can reverse age-related increases in myocardial stiffness (Erratum))

L3 ANSWER 45 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN
AB Decreased elasticity of the cardiovascular system is one of the hallmarks of the normal aging process of mammals. A potential explanation for this decreased elasticity is that glucose can react nonenzymically with long-lived proteins, such as collagen and lens crystallin, and link them together, producing advanced glycation endproducts (AGEs). Previous studies have shown that aminoguanidine, an AGE inhibitor, can prevent

glucose crosslinking of proteins and the loss of elasticity associated with aging and diabetes. Recently, an AGE cross-link breaker (ALT-711) has been described, which we have evaluated in aged dogs. After 1 mo of administration of ALT-711, a significant reduction (≈40%) in age-related left ventricular stiffness was observed [(57.1 ± 6.8 mmHg·m2/mL pretreatment and 33.1 ± 4.6 mmHg·m2/mL posttreatment (1 mmHg = 133 Pa))]. This decrease was accompanied by improvement in cardiac function.

2000:202230 Document Number 132:329694 An advanced glycation endproduct cross-link breaker can reverse age-related increases in myocardial stiffness. Asif, Mohammad; Egan, John; Vasan, Sara; Jyothirmayi, Garikiparthy N.; Masurekar, Malthi R.; Lopez, Santos; Williams, Chandra; Torres, Ramon L.; Wagle, Dilip; Ulrich, Peter; Cerami, Anthony; Brines, Michael; Regan, Timothy J. (University of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, NJ, 07103, USA). Proceedings of the National Academy of Sciences of the United States of America, 97(6), 2809-2813 (English) 2000. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

IT **181069-80-7**, ALT 711
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(an advanced glycation endproduct cross-link breaker can reverse age-related increases in myocardial stiffness)

L3 ANSWER 46 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN

AB Prolonged hyperglycemia inhibits B-cell function by mechanisms that are largely unclarified. We investigated the involvement of advanced glycation end products (AGEs), using aminoguanidine as well as the AGE-breaking compound ALT-711 in a transplantation model. Islets from Wistar-Furth rats were transplanted under the kidney capsule of syngeneic streptozocin-diabetic recipients. Aminoguanidine was administered as 1 g/L in the drinking water. Graft-bearing kidneys were isolated and perfused to investigate insulin secretion, and grafts were excised to measure preproinsulin mRNA contents. In all transplants to diabetic rats, insulin responses to 27.8 mM glucose were abolished and aminoguanidine failed to correct this abnormality. However, aminoguanidine treatment for 8 wk following transplantation increased preproinsulin mRNA contents of the grafts ($P < 0.05$). In addition, treatment with aminoguanidine enhanced the insulin secretory response to arginine ($P < 0.05$). Arginine-induced insulin secretion was also enhanced when aminoguanidine treatment was started after an initial 2-wk implantation period rather than immediately after transplantation. On the other hand, treatment with ALT-711 (0.1 mg/kg by gavage) for 8 wk completely failed to affect B-cell function of grafts, and ALT-711 was also ineffective under in vitro conditions. Our findings indicate that aminoguanidine effects in vivo are to a major extent not coupled to AGEs or nitric oxide synthetase inhibition, but possibly to oxidative modifications accomplished by the guanidine compound

2000:345369 Document Number 133:114896 Improvement by aminoguanidine of insulin secretion from pancreatic islets grafted to syngeneic diabetic rats. Hiramatsu, S.; Inoue, K.; Tajirl, Y.; Grill, V. (Endocrine and Diabetes Unit, Department of Molecular Medicine, Karolinska Hospital, Karolinska Institute, Stockholm, S-17176, Swed.). Biochemical Pharmacology, 60(2), 263-268 (English) 2000. CODEN: BCPCA6. ISSN: 0006-2952. Publisher: Elsevier Science Inc..

IT **181069-80-7**, ALT 711
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(improvement by aminoguanidine of insulin secretion from pancreatic islets grafted to syngeneic diabetic rats)

L3 ANSWER 47 OF 51 USPATFULL on STN

AB The present invention relates to compositions and methods for inhibiting and reversing nonenzymatic cross-linking (protein aging). Accordingly, compositions are disclosed which comprise an agent capable of inhibiting the formation of advanced glycosylation endproducts of target proteins, and which additionally reverse pre-formed crosslinks in the advanced glycosylation endproducts by cleaving alpha-dicarbonyl-based protein crosslinks present in the advanced glycosylation endproducts. Certain agents useful are thiazolium salts. The method comprises contacting the target protein with the composition. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A novel immunoassay for detection of the reversal of the nonenzymatic crosslinking is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

1999:170258 Reversing the formation of advanced glycosylation endproducts.
Cerami, Anthony, Shelter Island, NY, United States
Ulrich, Peter C., Old Tappan, NJ, United States
Wagle, Dilip R., Valley Cottage, NY, United States
Hwang, San-Bao, Sudbury, MA, United States
Vasan, Sara, Yonkers, NY, United States
Egan, John J., Mountain Lakes, NJ, United States
Alteon Inc., United States (U.S. corporation)The Picower Institute for Medical Research, United States (U.S. corporation)
US 6007865 19991228
APPLICATION: US 1997-971878 19971119 (8)
DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **181069-80-7P**
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

L3 ANSWER 48 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5

AB The present invention relates to compns. and methods for inhibiting and reversing nonenzymic crosslinking (protein aging). Accordingly, compns. are disclosed which comprise an agent capable of inhibiting the formation of advanced glycosylation endproducts of target proteins, and which addnl. reverse pre-formed crosslinks in the advanced glycosylation endproducts by cleaving alpha-dicarbonyl-based protein crosslinks present in the advanced glycosylation endproducts. Certain agents useful are thiazolium salts. The method comprises contacting the target protein with the composition Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A novel immunoassay for detection of the reversal of the nonenzymic crosslinking is also disclosed.

1999:25966 Document Number 130:100661 Thiazolium compounds for preventing and reversing the formation of advanced glycosylation endproducts. Cerami, Anthony; Ulrich, Peter C.; Wagle, Dilip R.; Hwang, San-Bao; Vasan, Sara; Egan, John J. (The Picower Institute for Medical Research, USA; Alteon Inc.). U.S. US 5853703 A 19981229, 30 pp., Cont.-in-part of U.S. Ser. Number 473,104, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1996-588249 19960118. PRIORITY: US 1995-375155 19950118; US 1995-473104 19950607.

IT **181069-80-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

L3 ANSWER 49 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN
AB Glucose and other reducing sugars react with proteins by a nonenzymic, posttranslational modification process called nonenzymic glycation. The formation of advanced glycation end products (AGEs) on connective tissue and matrix components accounts largely for the increase in collagen crosslinking that accompanies normal aging and which occurs at an accelerated rate in diabetes, leading to an increase in arterial stiffness. A new class of AGE crosslink "breakers" reacts with and cleaves these covalent, AGE-derived protein crosslinks. Treatment of rats with streptozotocin-induced diabetes with the AGE-breaker ALT-711 for 1-3 wk reversed the diabetes-induced increase of large artery stiffness as measured by systemic arterial compliance, aortic impedance, and carotid artery compliance and distensibility. These findings will have considerable implications for the treatment of patients with diabetes-related complications and aging.
1998:267333 Document Number 129:23234 Breakers of advanced glycation end products restore large artery properties in experimental diabetes. Wolffenbuttel, Bruce H. R.; Boulanger, Chantal M.; Crijns, Francy R. L.; Huijberts, Maya S. P.; Poitevin, Pierre; Swennen, Geertje N. M.; Vasan, Sara; Egan, John J.; Ulrich, Peter; Cerami, Anthony; Levy, Bernard I. (Department of Endocrinology, Cardiovascular Research Institute Maastricht and University (Hospital) Maastricht, Maastricht, 6202 AZ, Neth.). Proceedings of the National Academy of Sciences of the United States of America, 95(8), 4630-4634 (English) 1998. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.
IT **181069-80-7**, ALT 711
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(breakers of advanced glycation end products restore large artery properties in exptl. diabetes)

L3 ANSWER 50 OF 51 USPATFULL on STN
AB The present invention relates to compositions and methods for inhibiting and reversing nonenzymatic cross-linking (protein aging). Accordingly, a composition is disclosed which comprises a thiazolium compound capable of inhibiting, and to some extent reversing, the formation of advanced glycosylation endproducts of target proteins by reacting with the carbonyl moiety of the early glycosylation product of such target proteins formed by their initial glycosylation. The method comprises contacting the target protein with the composition. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A novel immunoassay for detection of the reversal of the nonenzymatic crosslinking is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
97:70708 Preventing and reversing advanced glycosylation endproducts.
Cerami, Anthony, Shelter Island, NY, United States

Ulrich, Peter C., Old Tappan, NJ, United States
Wagle, Dilip R., Valley Cottage, NY, United States
Hwang, San-Bao, Sudbury, MA, United States
Vasan, Sara, Yonkers, NY, United States
Egan, John J., Mountain Lakes, NJ, United States
The Picower Institute for Medical Research, Manhasset, NY, United States
(U.S. corporation)Alteon Inc., Ramsey, NJ, United States (U.S. corporation)
US 5656261 19970812
APPLICATION: US 1995-375155 19950118 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **181069-80-7P**
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

L3 ANSWER 51 OF 51 HCAPLUS COPYRIGHT 2006 ACS on STN
AB Compns. and methods for inhibiting and reversing nonenzymic crosslinking (protein aging) are disclosed. Accordingly, compositions are disclosed which comprise an agent capable of inhibiting the formation of advanced glycosylation endproducts of target proteins (such as thiazolium salts), and which addnl. reverse pre-formed crosslinks in the advanced glycosylation endproducts by cleaving α-dicarbonyl-based protein crosslinks present in the advanced glycosylation endproducts. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A novel immunoassay for detection of the reversal of the nonenzymic crosslinking is also disclosed. Thiazole 850 mg, Me bromoacetate 1.52 mg, and absolute ethanol 50 mL were refluxed for 2 h, then cooled and the salt separated and recrystd. to obtain 3-(2-methoxy-2-oxoethyl)-thiazolium bromide (I). A lotion contained I 1.0, ethanol 200.0, PEG-400 300.0, hydroxypropyl cellulose 5.0 mg, and propylene glycol q.s. 1.0 g.
1996:560531 Document Number 125:204548 Use of thiazolium compounds for preventing and reversing the formation of advanced glycosylation endproducts. Cerami, Anthony; Ulrich, Peter C.; Wagle, Dilip R.; Hwang, San-bao; Vasan, Sara; Egan, John J. (Alteon Inc., USA; The Picower Institute for Medical Research). PCT Int. Appl. WO 9622095 A2 19960725, 78 pp. DESIGNATED STATES: W: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, AZ, BY, KG, KZ, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US663 19960118. PRIORITY: US 1995-375155 19950118; US 1996-588249 19960118.
IT **181069-80-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); FFD (Food or feed use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

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     (FILE 'HOME' ENTERED AT 19:49:48 ON 04 JAN 2006)

     FILE 'REGISTRY' ENTERED AT 19:50:10 ON 04 JAN 2006
                E ALT 711/CN
L1             2 S E3

     FILE 'HCAPLUS, USPATFULL, USPAT2' ENTERED AT 19:51:19 ON 04 JAN 2006
L2            56 S L1
L3            51 DUP REM L2 (5 DUPLICATES REMOVED)

=> s l3 and hypertens?
L4            17 L3 AND HYPERTENS?

=> d l4 abs cbib kwic hitrn 1-17

L4   ANSWER 1 OF 17  HCAPLUS  COPYRIGHT 2006 ACS on STN
AB   A review. Advanced glycation end product (AGE) formation that occurs with
     aging and diabetes leads to the crosslinking of proteins and subsequent
     changes in the physicochem. properties of tissues. Cellular responses to
     AGE that lead to either pathol. conditions or removal of AGE are mediated
     by a number of receptors that have been identified on various cell types such
     as macrophages, endothelial cells, and smooth-muscle cells. Mechanisms by
     which AGE affect the cardiovascular system include AGE crosslinking of
     long-lived proteins such as collagen and elastin and altered cellular
     responses. Alagebrium (3-phenacyl-4,5-dimethylthiazolium chloride,
     ALT-711) is the first drug in a new class of thiazolium therapeutic agents
     that break established AGE cross-links between proteins. In animal
     studies, alagebrium was effective in reducing large artery stiffness,
     slowing pulse-wave velocity, enhancing cardiac output, and improving left
     ventricular diastolic distensibility. In human studies to determine safety and
     efficacy, alagebrium was safe and well tolerated. In the first phase 2
     clin. study, alagebrium improved arterial compliance in elderly patients
     with vascular stiffening. In two subsequent phase 2 clin. studies, one
     addressing diastolic heart failure and the other addressing systolic
     hypertension, alagebrium was effective in improving cardiac
     function and uncontrolled systolic blood pressure, particularly in more
     severely affected patients. Addnl. clin. studies to determine the utility of
     alagebrium in treating cardiovascular disorders associated with aging are in
     progress.
2004:1089059  Document Number 143:4826  Advanced glycation end-product cross-link
     breakers: A novel approach to cardiovascular pathologies related to the
     aging process. Bakris, George L.; Bank, Alan J.; Kass, David A.; Neutel,
     Joel M.; Preston, Richard A.; Oparil, Suzanne (Rush University Medical
     Center, Chicago, IL, USA). American Journal of Hypertension, 17(12, Pt.
     2), 23S-30S (English) 2004. CODEN: AJHYE6. ISSN: 0895-7061. Publisher:
     Elsevier Inc..
AB   . . . with vascular stiffening. In two subsequent phase 2 clin.
     studies, one addressing diastolic heart failure and the other addressing
     systolic hypertension, alagebrium was effective in improving
     cardiac function and uncontrolled systolic blood pressure, particularly in
     more severely affected patients. Addnl. clin.. . .
IT   Glycoproteins
     RL: ADV (Adverse effect, including toxicity); BSU (Biological study,
     unclassified); BIOL (Biological study)
```

(AGE (advanced glycosylation end product); phase 2 clin. study of alagebrium which break AGE cross-link between protein was effective, well tolerated in improving cardiac function by controlling systolic blood pressure, vascular stiffening, **hypertension** in elderly patient)

IT Blood pressure
Blood vessel, disease
Cardiovascular system, disease
Human
Hypertension
(phase 2 clin. study of alagebrium which break AGE cross-link between protein was effective, well tolerated in improving cardiac function by controlling systolic blood pressure, vascular stiffening, **hypertension** in elderly patient)

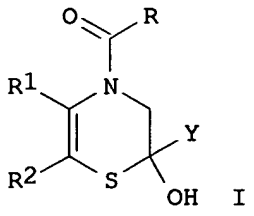
IT Diabetes mellitus
(phase 2 clin. study of alagebrium which break AGE cross-link formed in diabetes patient was effective, well tolerated in improving cardiac function by controlling systolic blood pressure, vascular stiffening, **hypertension**)

IT 28589-79-9, Thiazolium
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alagebrium class of thiazolium break AGE cross-link between protein was effective, well tolerated in improving cardiac function by controlling systolic blood pressure, vascular stiffening, **hypertension** in elderly patient)

IT **341028-37-3**, ALT-711
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phase 2 clin. study of ALT-711 which break AGE cross-link between protein was effective, well tolerated in improving cardiac function by controlling systolic blood pressure, vascular stiffening, **hypertension** in elderly patient)

IT **341028-37-3**, ALT-711
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phase 2 clin. study of ALT-711 which break AGE cross-link between protein was effective, well tolerated in improving cardiac function by controlling systolic blood pressure, vascular stiffening, **hypertension** in elderly patient)

L4 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
GI



I

AB The authors prepared thiazine compds. I [R = H, Me, HOCH2, MeCHOH; R1, R2 = H, C1-C6 alkyl, C1-C6 hydroxyalkyl, C3-C8 cycloalkyl, C1-C6 alkenyl, C1-C6 alkynyl, amino, monoalkylamino, dialkylaminoalkyl, pyrrolidin-1-ylalkyl; Y = C1-C6 alkyl, substituted and unsubstituted aryl; with the provisos that: (a) if Y = aryl, then at least one of R1 and R2 is other than H, and (b) if R2 = H, R1 = not Me] (and pharmaceutically acceptable salts thereof). For example, 4,5-dimethyl-3-(2-oxo-2-phenylethyl)thiazolium chloride was reacted with NaOH to give I (R = H, R1 = R2 = Me, Y = Ph). The compds. are useful, among other things, as prodrugs which can be converted under acidic conditions to thiazolium agents. The compds. can be administered to mammals, including humans, for treatment of various indications including **hypertension**, reduced vascular compliance, diastolic dysfunction, heart failure, and isolated systolic **hypertension**.

2004:927187 Document Number 141:395566 Preparaton of dihydrothiazine prodrugs of thiazolium agents. Reinhard, Emily; Katten, Elliot (Alteon, Inc., USA). PCT Int. Appl. WO 2004094396 A2 20041104, 40 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US11984 20040416. PRIORITY: US 2003-PV463807 20030418; US 2004-824848 20040415.

AB . . . acidic conditions to thiazolium agents. The compds. can be administered to mammals, including humans, for treatment of various indications including **hypertension**, reduced vascular compliance, diastolic dysfunction, heart failure, and isolated systolic **hypertension**.

ST thiazine prepn prodrug thiazolium salt **hypertension** heart failure; vascular compliance reduced thiazine prodrug thiazolium salt

IT Blood pressure
(diastolic; preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for **hypertension**, diastolic dysfunction, heart failure, and reduced vascular compliance)

IT Heart, disease
(failure; preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for **hypertension**, diastolic dysfunction, heart failure, and reduced vascular compliance)

IT **Hypertension**
(preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for **hypertension**, diastolic dysfunction, heart failure, and reduced vascular compliance)

IT Drug delivery systems
(prodrugs; preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for **hypertension**, diastolic dysfunction, heart failure, and reduced vascular compliance)

IT Blood pressure
(systolic; preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for **hypertension**, systolic **hypertension**, diastolic dysfunction, heart failure, and reduced vascular compliance)

IT Blood vessel, disease
(vascular compliance; preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for **hypertension**,

diastolic dysfunction, heart failure, and reduced vascular compliance)

IT 787621-17-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for **hypertension**, diastolic dysfunction, heart failure, and reduced vascular compliance)

IT 787621-19-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for **hypertension**, diastolic dysfunction, heart failure, and reduced vascular compliance)

IT **341028-37-3** 787621-18-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for **hypertension**, diastolic dysfunction, heart failure, and reduced vascular compliance)

IT 356758-28-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for **hypertension**, diastolic dysfunction, heart failure, and reduced vascular compliance)

IT **341028-37-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for **hypertension**, diastolic dysfunction, heart failure, and reduced vascular compliance)

L4 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN

AB Background: Increased formation of advanced glycosylation end-products on body proteins is a consequence of aging and leads to exaggerated collagen crosslinking eventually increasing cardiovascular stiffness. This study reports our initial inquires into the cardiovascular and renal effects of a cross-link breaker (ALT-711) in aged spontaneously **hypertensive** rats (SHR). Methods and results: The first experiment, in 45-wk-old SHR, showed that (among four doses) the dose of 1 mg/kg/d of ALT-711 given for 4 mo was most effective in reducing left ventricular and aortic mass indexes. ALT-711 also reduced left ventricular hydroxyproline concentration (5.8±0.2 v 5.1±0.3 mg/g in controls, P <.05); however, it did not affect systemic or regional hemodynamics. In older SHR, ALT-711 (1 mg/kg/d) reduced (P <.05) systolic pressure (tail-cuff) (from 203±3 mm Hg at outset to 187±3 mm Hg at 8 wk). Systolic pressure remained unchanged in placebo-treated rats. In addition, left ventricular index (3.09±0.10 v 3.44±0.05 mg/g) and aortic mass index (1.54±0.04 v 1.74±0.05 mg/mm) were reduced by ALT-711. In the third experiment, 1-yr-old SHR were given vehicle or ALT-711 (1 mg/kg/d) or placebo until natural death. After 3 mo, ALT-711 markedly reduced urinary protein excretion (74.5±8.6 v 135.4±11.8 mg/24 h). Echocardiog. studies, performed at the outset and after 3 and 6 mo, revealed two changed indexes. Left ventricular end-diastolic diameter increased more in control than in ALT rats, whereas E-wave deceleration time decreased more in control than in ALT rats. Conclusions: Therapy with ALT-711 exerted beneficial cardiovascular and renal effects in aged SHR, improving systolic pressure, left ventricular mass, geometry, and hydroxyproline content while reducing

urinary protein excretion.

2004:281528 Document Number 141:360381 Cardiovascular and renal effects of a collagen cross-link breaker (ALT 711) in adult and aged spontaneously **hypertensive** rats. Susic, Dinko; Varagic, Jasmina; Frohlich, Edward D. (Hypertension Research Laboratory, Ochsner Clinic Foundation, New Orleans, LA, USA). American Journal of Hypertension, 17(4), 328-333 (English) 2004. CODEN: AJHYE6. ISSN: 0895-7061. Publisher: Elsevier Science Inc..

TI Cardiovascular and renal effects of a collagen cross-link breaker (ALT 711) in adult and aged spontaneously **hypertensive** rats

AB . . . This study reports our initial inquires into the cardiovascular and renal effects of a cross-link breaker (ALT-711) in aged spontaneously **hypertensive** rats (SHR). Methods and results: The first experiment, in 45-wk-old SHR, showed that (among four doses) the dose of 1. . .

ST collagen cross link breaker cardiovascular renal system hemodynamics **hypertension**

IT **Hypertension**
(spontaneous; collagen cross-linker ALT 711 effectively reduced left ventricular and aortic indexes, left ventricular hydroxy proline content, systolic pressure, proteinuria, left ventricular diastolic diameter, E-wave deceleration in aged SHR)

IT **181069-80-7**, ALT 711
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(collagen cross-linker ALT 711 effectively reduced left ventricular and aortic indexes, left ventricular hydroxy proline content, systolic pressure, proteinuria, left ventricular diastolic diameter, E-wave deceleration in aged SHR)

IT **181069-80-7**, ALT 711
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(collagen cross-linker ALT 711 effectively reduced left ventricular and aortic indexes, left ventricular hydroxy proline content, systolic pressure, proteinuria, left ventricular diastolic diameter, E-wave deceleration in aged SHR)

L4 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN

AB A review. Long-lived structural proteins, collagen and elastin, undergo continual non-enzymic crosslinking during aging and in diabetic individuals. This abnormal protein crosslinking is mediated by advanced glycation end products (AGEs) generated by non-enzymic glycosylation of proteins by glucose. The AGE-derived protein crosslinking of structural proteins contributes to the complications of long-term diabetes such as nephropathy, retinopathy, and neuropathy. AGE-crosslinks have also been implicated in age-related cardiovascular diseases. Potential treatment strategies for these AGE-derived complications include prevention of AGE-formation and breaking of the existing AGE-crosslinks. The therapeutic potential of the AGE-inhibitor, pimagedine (aminoguanidine), has been extensively investigated in animal models and in Phase 3 clin. trials. This review presents the pre-clin. and clin. studies using ALT-711, a highly potent AGE-crosslink breaker that has the ability to reverse already-formed AGE-crosslinks. Oral administration of ALT-711 has resulted in a rapid improvement in the elasticity of stiffened myocardium in exptl. animals. Topical administration of ALT-711 was effective in improving the skin hydration of aged rats. The therapeutic potential of crosslink breakers for cardiovascular complications and dermatol. alterations associated with aging and diabetes is discussed.

2003:804088 Document Number 140:121913 Therapeutic potential of breakers of advanced glycation end product-protein crosslinks. Vasan, Sara; Foiles, Peter; Founds, Hank (Alteon Inc., Ramsey, NJ, 07446, USA). Archives of Biochemistry and Biophysics, 419(1), 89-96 (English) 2003. CODEN: ABBIA4. ISSN: 0003-9861. Publisher: Elsevier Science.

IT Aging, animal
Antihypertensives
Diabetes mellitus
Human
Hypertension
(therapeutic potential of AGE crosslink breakers)

IT **341028-37-3**, ALT 711
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT 711; therapeutic potential of AGE crosslink breakers)

IT **341028-37-3**, ALT 711
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT 711; therapeutic potential of AGE crosslink breakers)

L4 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN

AB Renal accumulation of advanced glycation end products (AGEs) has been linked to the progression of diabetic nephropathy. Cleavage of pre-formed AGEs within the kidney by a cross-link breaker, such as ALT-711, may confer renoprotection in diabetes. STZ diabetic rats were randomized into (a) no treatment (D); (b) treatment with the AGE cross-link breaker, ALT-711, weeks 16-32 (DALT early); and (c) ALT-711, weeks 24-32 (DALT late). Treatment with ALT-711 resulted in a significant reduction in diabetes-induced serum and renal AGE peptide fluorescence, associated with decreases in renal carboxymethyllysine and RAGE immunostaining. Crosslinking of tail tendon collagen seen in diabetic groups was attenuated only by 16 wk of ALT-711 treatment. ALT-711, independent of treatment duration, retarded albumin excretion rate (AER), reduced blood pressure, and renal hypertrophy. It also reduced diabetes-induced increases in gene expression of transforming growth factor β1 (TGF-β1), connective tissue growth factor (CTGF), and collagen IV. However, glomerulosclerotic index, tubulointerstitial area, total renal collagen, nitrotyrosine, protein expression of collagen IV, and TGF-β1 only showed improvement with early ALT treatment alone. This study demonstrates the utility of a cross-link breaker as a treatment for diabetic nephropathy and describes effects not only on renal AGEs but on putative mediators of renal injury, such as prosclerotic cytokines and oxidative stress.

2003:730751 Document Number 139:301751 The breakdown of pre-existing advanced glycation end products is associated with reduced renal fibrosis in experimental diabetes. Forbes, Josephine M.; Thallas, Vicki; Thomas, Merlin C.; Founds, Hank W.; Burns, Wendy C.; Jerums, George; Cooper, Mark E. (Division of Diabetic Complications, Baker Medical Research Institute, Melbourne, 8008, Australia). FASEB Journal, 17(12), 1762-1764, 10.1096/fj.02-1102fje (English) 2003. CODEN: FAJOEC. ISSN: 0892-6638. Publisher: Federation of American Societies for Experimental Biology.

IT **Hypertension**
Hypertrophy
(renal, reduction by cross-link breaker ALT-711; breakdown of pre-existing advanced glycation end products is associated with reduced renal fibrosis in exptl. diabetes)

IT **341028-37-3**, ALT 711

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT 711; breakdown of pre-existing advanced glycation end products is associated with reduced renal fibrosis in exptl. diabetes)

IT **341028-37-3**, ALT 711
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT 711; breakdown of pre-existing advanced glycation end products is associated with reduced renal fibrosis in exptl. diabetes)

L4 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN

AB Arterial stiffening with increased pulse pressure is a leading risk factor for cardiovascular disease in the elderly. We tested whether ALT-711, a novel nonenzymic breaker of advanced glycation end-product crosslinks, selectively improves arterial compliance and lowers pulse pressure in older individuals with vascular stiffening. Nine US centers recruited and randomly assigned subjects with resting arterial pulse pressures >60 mm Hg and systolic pressures >140 mm Hg to once-daily ALT-711 (210 mg; n=62) or placebo (n=31) for 56 days. Preexisting antihypertensive treatment (90% of subjects) was continued during the study. Morning upright blood pressure, stroke volume, cardiac output, systemic vascular resistance, total arterial compliance, carotid-femoral pulse wave velocity, and drug tolerability were assessed. ALT-711 netted a greater decline in pulse pressures than placebo (-5.3 vs. -0.6 mm Hg at day 56; P=0.034 for treatment effect by repeated-measures ANOVA). Systolic pressure declined in both groups, but diastolic pressure fell less with ALT-711 (P=0:056). Mean pressure declined similarly in both groups (-4 mm Hg; P<0.01 for each group, P=0.34 for treatment effect). Total arterial compliance rose 15% in ALT-711-treated subjects vs. no change with placebo (P=0.015 vs. ALT-711), an effect that did not depend on reduced mean pressure. Pulse wave velocity declined 8% with ALT-711 (P<0.05 at day 56, P=0.08 for treatment effect). Systemic arterial resistance, cardiac output, and heart rate did not significantly change in either group. ALT-711 improves total arterial compliance in aged humans with vascular stiffening, and it may provide a novel therapeutic approach for this abnormality, which occurs with aging, diabetes, and isolated systolic **hypertension**.

2001:783968 Document Number 136:112431 Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. Kass, David A.; Shapiro, Edward P.; Kawaguchi, Miho; Capriotti, Anne R.; Scuteri, Angelo; deGroof, Robert C.; Lakatta, Edward G. (Division of Cardiology, The Johns Hopkins Medical Institutions, Baltimore, MD, 21287, USA). Circulation, 104(13), 1464-1470 (English) 2001. CODEN: CIRCAZ. ISSN: 0009-7322. Publisher: Lippincott Williams & Wilkins.

AB . . . stiffening, and it may provide a novel therapeutic approach for this abnormality, which occurs with aging, diabetes, and isolated systolic **hypertension**.

IT **181069-80-7**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT 711; improved arterial compliance by a novel advanced glycation end-product crosslink breaker)

IT **181069-80-7**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT 711; improved arterial compliance by a novel advanced glycation end-product crosslink breaker)

L4 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
AB A review with 6 refs. Vascular and/or myocardial stiffness is a major problem in ageing, diabetes, **hypertension** and heart failure. The development of the stiffness is partly due to the formation of glucose-dependent cross-links in the collagen. ALT-711 cleaves these cross-links. In aged-rhesus monkeys, ALT-711 decreases vascular stiffness and this effect is reversible. ALT-711 also decreases myocardial stiffness in the monkeys but this effect is not reversible in 39 wk. ALT-711 has potential in the treatment of the stiffness associated with diabetes, **hypertension** and heart failure.
2001:321927 Document Number 135:131603 ALT-711 decreases cardiovascular stiffness and has potential in diabetes, **hypertension** and heart failure. Doggrell, Sheila A. (Doggrell Biomedical Communications, Auckland, N. Z.). Expert Opinion on Investigational Drugs, 10(5), 981-983 (English) 2001. CODEN: EOIDER. ISSN: 1354-3784. Publisher: Ashley Publications Ltd..
TI ALT-711 decreases cardiovascular stiffness and has potential in diabetes, **hypertension** and heart failure
AB A review with 6 refs. Vascular and/or myocardial stiffness is a major problem in ageing, diabetes, **hypertension** and heart failure. The development of the stiffness is partly due to the formation of glucose-dependent cross-links in the collagen.. . . this effect is not reversible in 39 wk. ALT-711 has potential in the treatment of the stiffness associated with diabetes, **hypertension** and heart failure.
ST review cardiovascular stiffness ALT711 diabetes **hypertension**; heart failure arterial stiffness ALT711 review
IT Aging, animal
Diabetes mellitus
Hypertension
(ALT-711 decreases cardiovascular stiffness and has potential in diabetes, **hypertension** and heart failure)
IT Heart, disease
(failure; ALT-711 decreases cardiovascular stiffness and has potential in diabetes, **hypertension** and heart failure)
IT Artery, disease
(stiffness; ALT-711 decreases cardiovascular stiffness and has potential in diabetes, **hypertension** and heart failure)
IT **341028-37-3**, ALT 711
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT-711 decreases cardiovascular stiffness and has potential in diabetes, **hypertension** and heart failure)
IT **341028-37-3**, ALT 711
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ALT-711 decreases cardiovascular stiffness and has potential in diabetes, **hypertension** and heart failure)

L4 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
AB Nonenzymic glycosylation and crosslinking of proteins by glucose contributes to an age-associated increase in vascular and myocardial stiffness. Some recently synthesized thiazolium compds. selectively break these protein cross-links, reducing collagen stiffness. We investigated the effects of 3-phenacyl-4,5-dimethylthiazolium chloride (ALT-711) on arterial and left ventricular (LV) properties and their coupling in old,

healthy, nondiabetic Macaca mulatta primates (age 21±3.6 yr). Serial measurements of arterial stiffness indexes [i.e., aortic pulse wave velocity (PWV) and augmentation (AGI) of carotid arterial pressure waveform] as well as echocardiog. detns. of LV structure and function were made before and for 39 wk after 11 i.m. injections of ALT-711 at 1.0 mg/kg body weight every other day. Heart rate, brachial blood pressure, and body weight were unchanged by the drug. PWV and AGI decreased to a nadir at 6 wk [PWV to 74.2±4.4% of baseline (B), P = 0.007; AGI to 41±7.3% of B, P = 0.046], and thereafter gradually returned to baseline. Concomitant increases in LV end diastolic diameter to 116.7±2.7% of B, P = 0.02; stroke volume index (SVindex) to 173.1±40.1% of B, P = 0.01; and systolic fractional shortening to 180±29.7% of B, P = 0.01 occurred after drug treatment The LV end systolic pressure/SVindex, an estimate of total LV vascular load, decreased to 60±12.1% of B (P = 0.02). The LV end systolic diameter/SVindex, an estimate of arterio-ventricular coupling, was improved (decreased to 54.3±11% of B, P < 0.002). Thus, in healthy older primates without diabetes, ALT-711 improved both arterial and ventricular function and optimized ventriculo-vascular coupling. This previously unidentified cross-link breaker may be an effective pharmacol. therapy to improve impaired cardiovascular function that occurs in the context of heart failure associated with aging, diabetes, or **hypertension**, conditions in which arterial and ventricular stiffness are increased.

2001:120548 Document Number 134:290192 A cross-link breaker has sustained effects on arterial and ventricular properties in older rhesus monkeys. Vaitkevicius, Peter V.; Lane, Mark; Spurgeon, Harold; Ingram, Donald K.; Roth, George S.; Egan, John J.; Vasan, Sara; Wagle, Dilip R.; Ulrich, Peter; Brines, Michael; Wuerth, Jean Paul; Cerami, Anthony; Lakatta, Edward G. (Intramural Research Program, Gerontology Research Center, National Institute on Aging, National Institutes of Health, Baltimore, MD, 21224, USA). Proceedings of the National Academy of Sciences of the United States of America, 98(3), 1171-1175 (English) 2001. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

AB . . . pharmacol. therapy to improve impaired cardiovascular function that occurs in the context of heart failure associated with aging, diabetes, or **hypertension**, conditions in which arterial and ventricular stiffness are increased.

IT **181069-80-7**, ALT-711
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of cross-link breaker on arterial and ventricular properties in aging rhesus monkeys)

IT **181069-80-7**, ALT-711
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of cross-link breaker on arterial and ventricular properties in aging rhesus monkeys)

L4 ANSWER 9 OF 17 USPATFULL on STN

AB In one embodiment, the present invention relates to compounds and compositions including pharmaceutical compositions containing the compounds and associated methods that uncouple sugar-mediated coupling of proteins, lipids, nucleic acids, and other biomaterials, and any combination thereof. In another embodiment, the compositions and associated methods have utility in vivo to reduce the deleterious

effects of sugar-mediated coupling processes in an organism, when the organism is exposed to the compound or composition internally, by ingestion, transdermal application, or other means. In yet another embodiment, the compositions and associated methods are useful for the ex-vivo treatment of organs, cells and tissues and external treatment of hair, nails and skin to rejuvenate them by changing deformability and increase the tissue diffusion coefficient. In a further embodiment, the present invention relates to novel compounds and pharmaceutical compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
2005:281557 Method and composition for rejuvinating cells, tissues organs, hair and nails.
Ulrich, Peter C., Portland, OR, UNITED STATES
Fang, Sheng Ding, Mount Kisco, NY, UNITED STATES
Brines, Michael L., Woodbridge, CT, UNITED STATES
Xie, Qiao-Wen, Yonkers, NY, UNITED STATES
Cerami, Anthony, Sleepy Hollow, NY, UNITED STATES
US 2005245512 A1 20051103
APPLICATION: US 2005-175098 A1 20050705 (11)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . and any combination thereof, such as retinopathy, cataracts, diabetic kidney disease, glomerulosclerosis, peripheral vascular disease, arteriosclerosis obliterans, peripheral neuropathy, stroke, **hypertension**, atherosclerosis, osteoarthritis, periarticular rigidity, loss of elasticity and wrinkling of skin, stiffening of joints, glomerulonephritis, urinary incontinence and obstruction, coronary. . .
DETD . . . (age-related)

	Diabetes-related	Diabetic retinopathy
Hearing	Age-related, degenerative	Presbyacusis
	Vascular (atherosclerosis-related)	Hearing loss
	Diabetes-related	Senso-neuronal hearing loss
Renal	Age-related, degenerative	Glomeruscierosis
	Vascular (atherosclerosis-related)	**Hypertensive** nephropathy
	Diabetes-related	Diabetic nephropathy

DETD . . . individuals over 60 years of age and is associated with exercise intolerance. Stiffening of the vasculature may induce isolated systolic **hypertension**, a major problem in elderly people. Isolated systolic **hypertension** is defined as a raised systolic pressure but normal diastolic pressure (i.e., increase in pulse pressure). It affects around half of people aged over 60 years (Ramsay L E et al. J Hum **Hypertens** 1999;13:569.92). Based on cross sectional, longitudinal, and randomised controlled trials, it is believed that isolated systolic **hypertension** confers a substantial cardiovascular risk (SHEP Cooperative Research Group. JAMA 1991;265:3255.65; Staessen J A, et al. Lancet 1997;350:757.64). In yet another embodiment of the present invention, a patient with diagnosed diastolic dysfunction and/or isolated systolic **hypertension** is treated with a medicament containing a composition of the present invention in an amount sufficient to exert clinical effectiveness.. . .
IT 81466-85-5 **341028-37-3** 446839-78-7
(preparation of azoles, azines and salts thereof for rejuvenating cells,

tissues, organs, hair and nails)
IT **341028-37-3**
(preparation of azoles, azines and salts thereof for rejuvenating cells, tissues, organs, hair and nails)

L4 ANSWER 10 OF 17 USPATFULL on STN
AB Provided are compounds of the formula (and pharmaceutically acceptable salts thereof): ##STR1##

wherein:

R is hydrogen, methyl, hydroxymethyl or α-hydroxyethyl;

R.sup.1 and R.sup.2 are independently selected from hydrogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 hydroxyalkyl, C.sub.3-C.sub.8 cycloalkyl, C.sub.1-C.sub.6 alkenyl, C.sub.1-C.sub.6 alkynyl, amino, monoalkylamino, dialkylaminoalkyl, and pyrrolidin-1-ylalkyl; and Y is selected from the group consisting of C.sub.1-C.sub.6 alkyl, substituted and unsubstituted aryl; with the provisos that: (a) if Y is aryl, then at least one of R.sup.1 and R.sup.2 is other than hydrogen, and (b) if R.sup.2 is hydrogen R.sup.1 is other than methyl.

Also provided are pharmaceutical compositions containing the compounds, and methods for the preparation of the compounds. The compounds are useful, among other things, as prodrugs which can be converted under acidic conditions to thiazolium agents. The compounds can be administered to mammals, including humans, for treatment of various indications.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
2005:17345 Dihydrothiazine prodrugs of thiazolium agents.
Reinhard, Emily, Ridgewood, NJ, UNITED STATES
Katten, Elliot, Flushing, NY, UNITED STATES
US 2005014747 A1 20050120
APPLICATION: US 2004-824848 A1 20040415 (10)
PRIORITY: US 2003-463807P 20030418 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . N-formyl and N-acyl dihydrothiazines can be administered to mammals, including humans for the treatment of a number of indications including **hypertension**, reduced vascular compliance, diastolic dysfunction and heart failure.
SUMM [0063] The indications of the invention that can be treated using the method described above include **hypertension** (e.g., isolated systolic **hypertension** and systolic **hypertension**), reduced vascular compliance, diastolic dysfunction and heart failure (including diastolic heart failure).
SUMM [0075] The indications of the invention that can be treated using the method described above include **hypertension** (e.g., isolated systolic **hypertension** and systolic **hypertension**), reduced vascular compliance, diastolic dysfunction and heart failure (including diastolic heart failure).
DETD [0099] **Hypertension**, Isolated Systolic **Hypertension**
DETD . . . to be important determinants of circulatory function. In elderly individuals, the loss of compliance in the aorta leads to systolic **hypertension** and isolated systolic **hypertension**, which in turn expands the arterial wall and

thereby diminishes the dynamic range of elasticity. In vivo studies in rodents,. . .

DETD [0101] Compared with that of a non-diabetic, the diabetic artery is smaller as it is stiffer. As in systolic **hypertension** and isolated systolic **hypertension** in which vessels stiffen with age and lose the dynamic range of expansion under systole. The compounds of the invention are used to treat, prevent, reduce or ameliorate **hypertension**, including systolic **hypertension**, isolated systolic **hypertension** and diabetic **hypertension**. Moreover, the same benefit is anticipated for the more rare **hypertensive** disorder, pulmonary **hypertension**. Pulmonary **hypertension** is a rare blood vessel disorder of the lung in which the pressure in the pulmonary artery (the blood vessel. . . similarity in development of elevated blood pressure in the pulmonary bed with the increase in systemic blood pressure in diabetic **hypertension** and in isolated systolic **hypertension** suggests similar mechanisms are involved.

DETD . . . The compounds of the invention are used to treat, prevent, reduce or ameliorate reduced vascular compliance, elevated pulse pressure, and **hypertension**. Moreover, the compounds are used to reduce pulse pressure, increase vascular compliance, or decrease the risk of death.

DETD [0104] Increased blood pressure can lead to the development of **hypertensive** encephalopathy. Compounds of the invention are used to treat, prevent, reduce or ameliorate **hypertensive** encephalopathy.

DETD . . . the heart, which occurs naturally with aging but more so in diabetes and in conditions of heart disorders such as **hypertension**, causes an increase in the distance between myocardial cells, leading to atrial fibrillation. Compounds of the invention are used to. . .

DETD . . . which is the process of increasing artery closure following an operation to open the artery, such as balloon angioplasty. Renovascular **hypertension** is the result of one or more of the renal arteries becoming partially or completely occluded. Compounds of the invention are used to treat, prevent, reduce or ameliorate restenosis and renovascular **hypertension**.

DETD . . . mg/24 h or .about.200 μg/min) that develops over a period of 10-15 years. In patients with type 1 diabetes, diabetic **hypertension** typically becomes manifest early on, by the time that patients develop microalbuminuria. Once overt nephropathy occurs, the glomerular filtration rate. . .

DETD [0189] In treating **hypertension**, heart failure, cardiomyopathy or heart attack, the compounds of the invention can be administered concurrently or in a combined formulation. . .

CLM What is claimed is:

31. The method of claim 30, wherein the indication is selected from **hypertension**, reduced vascular compliance, diastolic dysfunction and heart failure.

32. The method of claim 30, wherein the indication is **hypertension**.

33. The method of claim 32, wherein the **hypertension** is isolated systolic **hypertension**.

34. The method of claim 32, wherein the **hypertension** is

systolic **hypertension**.

44. The method of claim 39, wherein the indication is selected from **hypertension**, reduced vascular compliance, diastolic dysfunction and heart failure.

45. The method of claim 44, wherein the indication is **hypertension**.

46. The method of claim 45, wherein the **hypertension** is isolated systolic **hypertension**.

47. The method of claim 45, wherein the **hypertension** is systolic **hypertension**.

IT **341028-37-3** 787621-18-5
(preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for hypertension, diastolic dysfunction, heart failure, and reduced vascular compliance)

IT **341028-37-3**
(preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for hypertension, diastolic dysfunction, heart failure, and reduced vascular compliance)

L4 ANSWER 11 OF 17 USPATFULL on STN

AB The present invention relates to compositions and methods for inhibiting and reversing nonenzymatic cross-linking (protein aging). Accordingly, compositions are disclosed which comprise an agent capable of inhibiting the formation of advanced glycosylation endproducts of target proteins, and which additionally reverse pre-formed crosslinks in the advanced glycosylation endproducts by cleaving alpha-dicarbonyl-based protein crosslinks present in the advanced glycosylation endproducts. Certain useful agents are thiazolium salts. The method comprises contacting the target protein with the composition. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A novel immunoassay for detection of the reversal of the nonenzymatic crosslinking is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

2004:45081 Preventing and reversing the formation of advance glycosylation endproducts.
Cerami, Anthony, Shelter Island, NY, UNITED STATES
Ulrich, Peter C., Old Tappan, NJ, UNITED STATES
Wagle, Dilip R., Valley Cottage, NY, UNITED STATES
Hwang, San-Bao, Sudbury, MA, UNITED STATES
Vasan, Sara, Yonkers, NY, UNITED STATES
Egan, John J., Mountain Lakes, NJ, UNITED STATES
US 2004034074 A1 20040219
APPLICATION: US 2003-418398 A1 20030418 (10)
DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . by cross-linked target proteins, such as retinopathy, cataracts, diabetic kidney disease, glomerulosclerosis, peripheral vascular disease, arteriosclerosis obliterans, peripheral neuropathy, stroke, **hypertension**, atherosclerosis, osteoarthritis, periarticular rigidity, loss of elasticity and wrinkling of skin,

stiffening of joints, glomeruloneplritis, etc. Likewise, all of these. . .

CLM What is claimed is:
13. A method for treating or ameliorating **hypertension** in an animal, said method comprising administering a **hypertension** treating or ameliorating effective amount of a pharmaceutical composition, said pharmaceutical composition comprising the compound of claim 1 and a. . .

IT 4568-71-2P 5304-34-7P 6274-00-6P 7467-00-7P 7478-09-3P
16311-69-6P 52197-73-6P 53995-67-8P 54016-70-5P 57132-40-8P
57168-49-7P 57168-62-4P 61544-06-7P 74360-51-3P 74385-09-4P
87910-71-2P 97380-14-8P 121704-45-8P 132416-79-6P 138404-41-8P
159356-41-9P 181069-78-3P 181069-79-4P **181069-80-7P**
181069-81-8P 181069-82-9P 181069-83-0P 181069-84-1P 181069-85-2P
181069-86-3P 181069-89-6P 181069-90-9P 181069-91-0P 181069-92-1P
181069-93-2P 181069-95-4P 181069-96-5P 181069-98-7P 181069-99-8P
181070-00-8P 181070-03-1P 181070-04-2P 181070-05-3P 181070-06-4P
181070-07-5P 181070-08-6P 181070-09-7P 181070-10-0P 181070-11-1P
181070-12-2P 181070-13-3P 181070-14-4P 181070-15-5P 181070-16-6P
181070-18-8P 181070-22-4P 181070-24-6P 181070-25-7P 181070-26-8P
181070-27-9P 181070-28-0P 181070-29-1P 181070-30-4P 181070-31-5P
181070-33-7P 181070-35-9P 181070-36-0P 181070-37-1P 181070-38-2P
181070-39-3P 181070-40-6P 181070-41-7P 181070-43-9P 181070-44-0P
181070-46-2P 181070-48-4P 181070-49-5P 181070-50-8P 181070-51-9P
181070-52-0P 181070-53-1P 181070-54-2P 181070-55-3P 181070-56-4P
181070-57-5P 181070-58-6P 181070-59-7P 181070-60-0P 181070-61-1P
181070-62-2P 181070-63-3P 181070-64-4P 181070-65-5P 181070-66-6P
181070-67-7P 181070-68-8P 181070-69-9P 181070-70-2P 181070-71-3P
181070-72-4P 181070-74-6P 181147-74-0P
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

IT **181069-80-7P**
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

L4 ANSWER 12 OF 17 USPATFULL on STN

AB The present invention relates to compositions and methods for inhibiting and reversing nonenzymatic cross-linking (protein aging). Accordingly, a composition is disclosed which comprises a thiazolium compound capable of inhibiting, and to some extent reversing, the formation of advanced glycosylation endproducts of target proteins by reacting with the carbonyl moiety of the early glycosylation product of such target proteins formed by their initial glycosylation. The method comprises contacting the target protein with the composition. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A novel immunoassay for detection of the reversal of the nonenzymatic crosslinking is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

2003:308308 Preventing and reversing advanced glycosylation endproducts.
Cerami, Anthony, Shelter Island, NY, United States
Ulrich, Peter C., Old Tappan, NJ, United States
Wagle, Dilip R., Valley Cottage, NY, United States
Hwang, San-Bao, Sudbury, MA, United States
Vasan, Sara, Yonkers, NY, United States

Egan, John J., New York City, NY, United States
Alteon Inc., Ramsey, NJ, United States (U.S. corporation)
US 38330 E1 20031125
US 5656261 19970812 (Original)
APPLICATION: US 1999-373345 19990812 (9)
US 1995-375155 19950118 (Original)
DOCUMENT TYPE: Reissue; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . by cross-linked target proteins, such as retinopathy, cataracts, diabetic kidney disease, glomerulosclerosis, peripheral vascular disease, arteriosclerosis obliterans, peripheral neuropathy, stroke, **hypertension**, atherosclerosis, osteoarthritis, periarticular rigidity, loss of elasticity and wrinkling of skin, stiffening of joints, glomerulonephritis, etc. Likewise, all of these. . .

CLM What is claimed is:
107. A method of treating or ameliorating **hypertension** in an animal, said method comprising administering an **hypertension** treating or ameliorating effective amount of a pharmaceutical composition, said pharmaceutical composition comprising one or more compounds selected from compounds. . .
118. The method of claim 107, comprising treating or ameliorating **hypertension** in a human.

IT 4568-71-2P 5304-34-7P 6274-00-6P 7467-00-7P 7478-09-3P
16311-69-6P 52197-73-6P 53995-67-8P 54016-70-5P 57132-40-8P
57168-49-7P 57168-62-4P 61544-06-7P 74360-51-3P 74385-09-4P
87910-71-2P 97380-14-8P 121704-45-8P 132416-79-6P 138404-41-8P
159356-41-9P 181069-78-3P 181069-79-4P **181069-80-7P**
181069-81-8P 181069-82-9P 181069-83-0P 181069-84-1P 181069-85-2P
181069-86-3P 181069-89-6P 181069-90-9P 181069-91-0P 181069-92-1P
181069-93-2P 181069-95-4P 181069-96-5P 181069-98-7P 181069-99-8P
181070-00-8P 181070-03-1P 181070-04-2P 181070-05-3P 181070-06-4P
181070-07-5P 181070-08-6P 181070-09-7P 181070-10-0P 181070-11-1P
181070-12-2P 181070-13-3P 181070-14-4P 181070-15-5P 181070-16-6P
181070-18-8P 181070-22-4P 181070-24-6P 181070-25-7P 181070-26-8P
181070-27-9P 181070-28-0P 181070-29-1P 181070-30-4P 181070-31-5P
181070-33-7P 181070-35-9P 181070-36-0P 181070-37-1P 181070-38-2P
181070-39-3P 181070-40-6P 181070-41-7P 181070-43-9P 181070-44-0P
181070-46-2P 181070-48-4P 181070-49-5P 181070-50-8P 181070-51-9P
181070-52-0P 181070-53-1P 181070-54-2P 181070-55-3P 181070-56-4P
181070-57-5P 181070-58-6P 181070-59-7P 181070-60-0P 181070-61-1P
181070-62-2P 181070-63-3P 181070-64-4P 181070-65-5P 181070-66-6P
181070-67-7P 181070-68-8P 181070-69-9P 181070-70-2P 181070-71-3P
181070-72-4P 181070-74-6P 181147-74-0P
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

IT **181069-80-7P**
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)
|

L4 ANSWER 13 OF 17 USPATFULL on STN
AB The present invention relates to compositions and methods for inhibiting and reversing nonenzymatic cross-linking (protein aging). Accordingly, compositions are disclosed which comprise an agent capable of inhibiting the formation of advanced glycosylation endproducts of target proteins,

and which additionally reverse pre-formed crosslinks in the advanced glycosylation endproducts by cleaving alpha-dicarbonyl-based protein crosslinks present in the advanced glycosylation endproducts. Certain agents useful are thiazolium salts. The method comprises contacting the target protein with the composition. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A novel immunoassay for detection of the reversal of the nonenzymatic crosslinking is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
2002:337482 Method of treating certain indications associated with hyperglycemia.
Cerami, Anthony, Shelter Island, NY, UNITED STATES
Ulrich, Peter C., Old Tappan, NJ, UNITED STATES
Wagle, Dilip R., Valley Cottage, NY, UNITED STATES
Hwang, San-Bao, Sudbury, MA, UNITED STATES
Vasan, Sara, Yonkers, NY, UNITED STATES
Egan, John J., Mountain Lakes, NJ, UNITED STATES
US 2002192842 A1 20021219
APPLICATION: US 2002-174883 A1 20020619 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . by cross-linked target proteins, such as retinopathy, cataracts, diabetic kidney disease, glomerulosclerosis, peripheral vascular disease, arteriosclerosis obliterans, peripheral neuropathy, stroke, **hypertension**, atherosclerosis, osteoarthritis, periarticular rigidity, loss of elasticity and wrinkling of skin, stiffening of joints, glomerulonephritis, etc. Likewise, all of these. . .

IT 4568-71-2P 5304-34-7P 6274-00-6P 7467-00-7P 7478-09-3P
16311-69-6P 52197-73-6P 53995-67-8P 54016-70-5P 57132-40-8P
57168-49-7P 57168-62-4P 61544-06-7P 74360-51-3P 74385-09-4P
87910-71-2P 97380-14-8P 121704-45-8P 132416-79-6P 138404-41-8P
159356-41-9P 181069-78-3P 181069-79-4P **181069-80-7P**
181069-81-8P 181069-82-9P 181069-83-0P 181069-84-1P 181069-85-2P
181069-86-3P 181069-89-6P 181069-90-9P 181069-91-0P 181069-92-1P
181069-93-2P 181069-95-4P 181069-96-5P 181069-98-7P 181069-99-8P
181070-00-8P 181070-03-1P 181070-04-2P 181070-05-3P 181070-06-4P
181070-07-5P 181070-08-6P 181070-09-7P 181070-10-0P 181070-11-1P
181070-12-2P 181070-13-3P 181070-14-4P 181070-15-5P 181070-16-6P
181070-18-8P 181070-22-4P 181070-24-6P 181070-25-7P 181070-26-8P
181070-27-9P 181070-28-0P 181070-29-1P 181070-30-4P 181070-31-5P
181070-33-7P 181070-35-9P 181070-36-0P 181070-37-1P 181070-38-2P
181070-39-3P 181070-40-6P 181070-41-7P 181070-43-9P 181070-44-0P
181070-46-2P 181070-48-4P 181070-49-5P 181070-50-8P 181070-51-9P
181070-52-0P 181070-53-1P 181070-54-2P 181070-55-3P 181070-56-4P
181070-57-5P 181070-58-6P 181070-59-7P 181070-60-0P 181070-61-1P
181070-62-2P 181070-63-3P 181070-64-4P 181070-65-5P 181070-66-6P
181070-67-7P 181070-68-8P 181070-69-9P 181070-70-2P 181070-71-3P
181070-72-4P 181070-74-6P 181147-74-0P
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

IT **181069-80-7P**
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

L4 ANSWER 14 OF 17 USPATFULL on STN

AB In one embodiment, the present invention relates to compounds and compositions including pharmaceutical compositions containing the compounds and associated methods that uncouple sugar-mediated coupling of proteins, lipids, nucleic acids, and other biomaterials, and any combination thereof. In another embodiment, the compositions and associated methods have utility in vivo to reduce the deleterious effects of sugar-mediated coupling processes in an organism, when the organism is exposed to the compound or composition internally, by ingestion, transdermal application, or other means. In yet another embodiment, the compositions and associated methods are useful for the ex-vivo treatment of organs, cells and tissues and external treatment of hair, nails and skin to rejuvenate them by changing deformability and increase the tissue diffusion coefficient. In a further embodiment, the present invention relates to novel compounds and pharmaceutical compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

2002:330330 Method and composition for rejuvinating cells, tissues organs, hair and nails.

Ulrich, Peter C., Portland, OR, UNITED STATES
Fang, Sheng Ding, Mount Kisco, NY, UNITED STATES
Brines, Michael L., Woodbridge, CT, UNITED STATES
Xie, Qiao-Wen, Yonkers, NY, UNITED STATES
Cerami, Anthony, Sleepy Hollow, NY, UNITED STATES

US 2002188015 A1 20021212
APPLICATION: US 2002-72712 A1 20020207 (10)
PRIORITY: US 2001-267226P 20010207 (60)
DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and any combination thereof, such as retinopathy, cataracts, diabetic kidney disease, glomerulosclerosis, peripheral vascular disease, arteriosclerosis obliterans, peripheral neuropathy, stroke, **hypertension**, atherosclerosis, osteoarthritis, periarticular rigidity, loss of elasticity and wrinkling of skin, stiffening of joints, glomerulonephritis, urinary incontinence and obstruction, coronary. . .

SUMM . . . (age-related)

	Diabetes-related	Diabetic retinopathy
Hearing	Age-related, degenerative	Presbyacusis
	Vascular (atherosclerosis-related)	Hearing loss
	Diabetes-related	Senso-neuronal hearing loss
Renal	Age-related, degenerative	Glomerusclerosis
	Vascular (atherosclerosis-related)	**Hypertensive** nephropathy
	Diabetes-related	Diabetic nephropathy

DETD . . . individuals over 60 years of age and is associated with exercise intolerance. Stiffening of the vasculature may induce isolated systolic **hypertension**, a major problem in elderly people. Isolated systolic **hypertension** is defined as a raised systolic pressure but normal diastolic pressure (i.e., increase in pulse pressure). It affects around half of people aged over 60 years (Ramsay L E et al. J Hum **Hypertens** 1999; 13:569.92). Based on cross sectional, longitudinal, and randomised controlled trials, it is believed that isolated systolic **hypertension** confers a substantial cardiovascular risk (SHEP Cooperative Research Group. JAMA 1991;265:3255.65; Staessen J A, et al. Lancet 1997;350:757.64). In yet

another embodiment of the present invention, a patient with diagnosed diastolic dysfunction and/or isolated systolic **hypertension** is treated with a medicament containing a composition of the present invention in an amount sufficient to exert clinical effectiveness.. . .

IT 81466-85-5 **341028-37-3** 446839-78-7
(preparation of azoles, azines and salts thereof for rejuvenating cells, tissues, organs, hair and nails)

IT **341028-37-3**
(preparation of azoles, azines and salts thereof for rejuvenating cells, tissues, organs, hair and nails)

L4 ANSWER 15 OF 17 USPATFULL on STN

AB The present invention relates to compositions and methods for inhibiting and reversing nonenzymatic cross-linking (protein aging). Accordingly, compositions are disclosed which comprise an agent capable of inhibiting the formation of advanced glycosylation endproducts of target proteins, and which additionally reverse pre-formed crosslinks in the advanced glycosylation endproducts by cleaving alpha-dicarbonyl-based protein crosslinks present in the advanced glycosylation endproducts. Certain agents useful are thiazolium salts. The method comprises contacting the target protein with the composition. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A immunoassay for detection of the reversal of the nonenzymatic crosslinking is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

2002:217094 Method of treating certain indications associated with hyperglycemia.
Cerami, Anthony, Shelter Island, NY, United States
Ulrich, Peter C., Old Tappan, NJ, United States
Wagle, Dilip R., Valley Cottage, NY, United States
Hwang, San-Bao, Sudbury, MA, United States
Vasan, Sara, Yonkers, NY, United States
Egan, John J., Mountain Lakes, NJ, United States
Alteon. Inc., Ramsey, NJ, United States (U.S. corporation)The Picower Institute for Medical Research, Manhasset, NY, United States (U.S. corporation)
US 6440749 B1 20020827
APPLICATION: US 1999-470482 19991222 (9)
DOCUMENT TYPE: Utility; GRANTED.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . by cross-linked target proteins, such as retinopathy, cataracts, diabetic kidney disease, glomerulosclerosis, peripheral vascular disease, arteriosclerosis obliterans, peripheral neuropathy, stroke, **hypertension**, atherosclerosis, osteoarthritis, periarticular rigidity, loss of elasticity and wrinkling of skin, stiffening of joints, glomerulonephritis, etc. Likewise, all of these. . .

CLM What is claimed is:

. . . or treating or ameliorating (ii) adverse sequelae of diabetes, (iii) kidney damage, (iv) damage to blood vasculature or atherosclerosis, (v) **hypertension**, (vi) retinopathy, (vii) peripheral neuropathy, (viii) cataracts, (ix) osteoarthritis, (x) Alzheimer's disease or (xi) damage to a tissue caused by. . .

6. The method of claim 1, wherein the method is for treating or ameliorating (v) **hypertension**.

25. A method of, in an animal, treating (i) diabetes or treating or ameliorating (ii) adverse sequelae of diabetes, (iii) kidney damage, (iv) damage to blood vasculature or atherosclerosis, (v) **hypertension**, (vi) retinopathy, (vii) peripheral neuropathy, (viii) cataracts, (ix) osteoarthritis, (x) Alzheimer's disease or (xi) damage to a tissue caused by. . .
30. The method of claim 25, wherein the method is for treating or ameliorating (v) **hypertension**.

39. A method, in an animal, treating (i) diabetes or treating or ameliorating (ii) adverse sequelae of diabetes, (iii) kidney damage, (iv) damage to blood vasculature or atherosclerosis, (v) **hypertension**, (vi) retinopathy, (vii) peripheral neuropathy, (viii) cataracts, (ix) osteoarthritis, (x) Alzheimer's disease or (xi) damage to a tissue caused by. . .
47. The method of claim 39, wherein the method is for treating or ameliorating (v) **hypertension**.

IT 4568-71-2P 5304-34-7P 6274-00-6P 7467-00-7P 7478-09-3P
16311-69-6P 52197-73-6P 53995-67-8P 54016-70-5P 57132-40-8P
57168-49-7P 57168-62-4P 61544-06-7P 74360-51-3P 74385-09-4P
87910-71-2P 97380-14-8P 121704-45-8P 132416-79-6P 138404-41-8P
159356-41-9P 181069-78-3P 181069-79-4P **181069-80-7P**
181069-81-8P 181069-82-9P 181069-83-0P 181069-84-1P 181069-85-2P
181069-86-3P 181069-89-6P 181069-90-9P 181069-91-0P 181069-92-1P
181069-93-2P 181069-95-4P 181069-96-5P 181069-98-7P 181069-99-8P
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181070-07-5P 181070-08-6P 181070-09-7P 181070-10-0P 181070-11-1P
181070-12-2P 181070-13-3P 181070-14-4P 181070-15-5P 181070-16-6P
181070-18-8P 181070-22-4P 181070-24-6P 181070-25-7P 181070-26-8P
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181070-33-7P 181070-35-9P 181070-36-0P 181070-37-1P 181070-38-2P
181070-39-3P 181070-40-6P 181070-41-7P 181070-43-9P 181070-44-0P
181070-46-2P 181070-48-4P 181070-49-5P 181070-50-8P 181070-51-9P
181070-52-0P 181070-53-1P 181070-54-2P 181070-55-3P 181070-56-4P
181070-57-5P 181070-58-6P 181070-59-7P 181070-60-0P 181070-61-1P
181070-62-2P 181070-63-3P 181070-64-4P 181070-65-5P 181070-66-6P
181070-67-7P 181070-68-8P 181070-69-9P 181070-70-2P 181070-71-3P
181070-72-4P 181070-74-6P 181147-74-0P
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)
IT **181069-80-7P**
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)
|

L4 ANSWER 16 OF 17 USPATFULL on STN
AB The present invention relates to compositions and methods for inhibiting and reversing nonenzymatic cross-linking (protein aging). Accordingly, compositions are disclosed which comprise an agent capable of inhibiting the formation of advanced glycosylation endproducts of target proteins, and which additionally reverse pre-formed crosslinks in the advanced glycosylation endproducts by cleaving alpha-dicarbonyl-based protein crosslinks present in the advanced glycosylation endproducts. Certain agents useful are thiazolium salts. The method comprises contacting the target protein with the composition. Both industrial and therapeutic

applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A novel immunoassay for detection of the reversal of the nonenzymatic crosslinking is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
1999:170258 Reversing the formation of advanced glycosylation endproducts.
Cerami, Anthony, Shelter Island, NY, United States
Ulrich, Peter C., Old Tappan, NJ, United States
Wagle, Dilip R., Valley Cottage, NY, United States
Hwang, San-Bao, Sudbury, MA, United States
Vasan, Sara, Yonkers, NY, United States
Egan, John J., Mountain Lakes, NJ, United States
Alteon Inc., United States (U.S. corporation)The Picower Institute for Medical Research, United States (U.S. corporation)
US 6007865 19991228
APPLICATION: US 1997-971878 19971119 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . by cross-linked target proteins, such as retinopathy, cataracts, diabetic kidney disease, glomerulosclerosis, peripheral vascular disease, arteriosclerosis obliterans, peripheral neuropathy, stroke, **hypertension**, atherosclerosis, osteoarthritis, periarticular rigidity, loss of elasticity and wrinkling of skin, stiffening of joints, glomerulonephritis, etc. Likewise, all of these.
. .
IT 4568-71-2P 5304-34-7P 6274-00-6P 7467-00-7P 7478-09-3P
16311-69-6P 52197-73-6P 53995-67-8P 54016-70-5P 57132-40-8P
57168-49-7P 57168-62-4P 61544-06-7P 74360-51-3P 74385-09-4P
87910-71-2P 97380-14-8P 121704-45-8P 132416-79-6P 138404-41-8P
159356-41-9P 181069-78-3P 181069-79-4P **181069-80-7P**
181069-81-8P 181069-82-9P 181069-83-0P 181069-84-1P 181069-85-2P
181069-86-3P 181069-89-6P 181069-90-9P 181069-91-0P 181069-92-1P
181069-93-2P 181069-95-4P 181069-96-5P 181069-98-7P 181069-99-8P
181070-00-8P 181070-03-1P 181070-04-2P 181070-05-3P 181070-06-4P
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181070-18-8P 181070-22-4P 181070-24-6P 181070-25-7P 181070-26-8P
181070-27-9P 181070-28-0P 181070-29-1P 181070-30-4P 181070-31-5P
181070-33-7P 181070-35-9P 181070-36-0P 181070-37-1P 181070-38-2P
181070-39-3P 181070-40-6P 181070-41-7P 181070-43-9P 181070-44-0P
181070-46-2P 181070-48-4P 181070-49-5P 181070-50-8P 181070-51-9P
181070-52-0P 181070-53-1P 181070-54-2P 181070-55-3P 181070-56-4P
181070-57-5P 181070-58-6P 181070-59-7P 181070-60-0P 181070-61-1P
181070-62-2P 181070-63-3P 181070-64-4P 181070-65-5P 181070-66-6P
181070-67-7P 181070-68-8P 181070-69-9P 181070-70-2P 181070-71-3P
181070-72-4P 181070-74-6P 181147-74-0P
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)
IT **181069-80-7P**
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

L4 ANSWER 17 OF 17 USPATFULL on STN
AB The present invention relates to compositions and methods for inhibiting and reversing nonenzymatic cross-linking (protein aging). Accordingly, a composition is disclosed which comprises a thiazolium compound capable of inhibiting, and to some extent reversing, the formation of advanced

glycosylation endproducts of target proteins by reacting with the carbonyl moiety of the early glycosylation product of such target proteins formed by their initial glycosylation. The method comprises contacting the target protein with the composition. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated. A novel immunoassay for detection of the reversal of the nonenzymatic crosslinking is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
97:70708 Preventing and reversing advanced glycosylation endproducts.
Cerami, Anthony, Shelter Island, NY, United States
Ulrich, Peter C., Old Tappan, NJ, United States
Wagle, Dilip R., Valley Cottage, NY, United States
Hwang, San-Bao, Sudbury, MA, United States
Vasan, Sara, Yonkers, NY, United States
Egan, John J., Mountain Lakes, NJ, United States
The Picower Institute for Medical Research, Manhasset, NY, United States (U.S. corporation)Alteon Inc., Ramsey, NJ, United States (U.S. corporation)
US 5656261 19970812
APPLICATION: US 1995-375155 19950118 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . by cross-linked target proteins, such as retinopathy, cataracts, diabetic kidney disease, glomerulosclerosis, peripheral vascular disease, arteriosclerosis obliterans, peripheral neuropathy, stroke, **hypertension**, atherosclerosis, osteoarthritis, periarticular rigidity, loss of elasticity and wrinkling of skin, stiffening of joints, glomerulonephritis, etc. Likewise, all of these.
. .
IT 4568-71-2P 5304-34-7P 6274-00-6P 7467-00-7P 7478-09-3P
16311-69-6P 52197-73-6P 53995-67-8P 54016-70-5P 57132-40-8P
57168-49-7P 57168-62-4P 61544-06-7P 74360-51-3P 74385-09-4P
87910-71-2P 97380-14-8P 121704-45-8P 132416-79-6P 138404-41-8P
159356-41-9P 181069-78-3P 181069-79-4P **181069-80-7P**
181069-81-8P 181069-82-9P 181069-83-0P 181069-84-1P 181069-85-2P
181069-86-3P 181069-89-6P 181069-90-9P 181069-91-0P 181069-92-1P
181069-93-2P 181069-95-4P 181069-96-5P 181069-98-7P 181069-99-8P
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181070-07-5P 181070-08-6P 181070-09-7P 181070-10-0P 181070-11-1P
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181070-33-7P 181070-35-9P 181070-36-0P 181070-37-1P 181070-38-2P
181070-39-3P 181070-40-6P 181070-41-7P 181070-43-9P 181070-44-0P
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181070-52-0P 181070-53-1P 181070-54-2P 181070-55-3P 181070-56-4P
181070-57-5P 181070-58-6P 181070-59-7P 181070-60-0P 181070-61-1P
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181070-67-7P 181070-68-8P 181070-69-9P 181070-70-2P 181070-71-3P
181070-72-4P 181070-74-6P 181147-74-0P
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)
IT **181069-80-7P**
(use of thiazolium compds. for preventing and reversing the formation of advanced glycosylation endproducts)

09/905,188

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DELACROIX

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=> s hydrochlorothiazid?
L5        6447 HYDROCHLOROTHIAZID?

=> d his

     (FILE 'HOME' ENTERED AT 19:49:48 ON 04 JAN 2006)

     FILE 'REGISTRY' ENTERED AT 19:50:10 ON 04 JAN 2006
                E ALT 711/CN
L1            2 S E3

     FILE 'HCAPLUS, USPATFULL, USPAT2' ENTERED AT 19:51:19 ON 04 JAN 2006
L2           56 S L1
L3           51 DUP REM L2 (5 DUPLICATES REMOVED)
L4           17 S L3 AND HYPERTENS?
L5         6447 S HYDROCHLOROTHIAZID?

=> s l5 and l3
L6            3 L5 AND L3

=> d l6 abs cbib kwic hitrn 1-3

L6   ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2006 ACS on STN
AB   Claimed are compns. comprising a polypeptide and an active agent
     covalently attached to the polypeptide and a method for delivery of an
     active agent to a patient by administering the composition to the patient.  The
     peptide is a homopolymer of a naturally occurring amino acid or a
     heteropolymer of two or more naturally occurring amino acids.  In an
     example, (Glu)n-cephalexin was prepared from Glu(OBut)NCA and cephalexin
     hydrochloride.
2002:556104   Document Number 137:109489  Compositions comprising a polypeptide
     and an active agent.  Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randal
     J. (USA).  U.S. Pat. Appl. Publ. US 2002099013 A1 20020725, 34 pp.
     (English).  CODEN: USXXCO.  APPLICATION: US 2001-933708 20010822.
     PRIORITY: US 2000-2000/PV247928; 20001114; US 2000-2000/PV247621;
     20001114; US 2000-2000/PV247620; 20001114; US 2000-2000/PV247595;
     20001114; US 2000-2000/PV247594; 20001114; US 2000-2000/PV247635;
     20001114; US 2000-2000/PV247634; 20001114; US 2000-2000/PV247606;
     20001114; US 2000-2000/PV247607; 20001114; US 2000-2000/PV247608;
     20001114; US 2000-2000/PV247609; 20001114; US 2000-2000/PV247610;
     20001114; US 2000-2000/PV247611; 20001114; US 2000-2000/PV247702;
     20001114; US 2000-2000/PV247701; 20001114; US 2000-2000/PV247700;
     20001114; US 2000-2000/PV247699; 20001114; US 2000-2000/PV247698;
     20001114; US 2000-2000/PV247807; 20001114; US 2000-2000/PV247833;
     20001114.
IT   50-06-6, Phenobarbital, biological studies   50-18-0, Cyclophosphamide
     50-35-1, Thalidomide   50-44-2, Mercaptopurine   50-78-2, Acetylsalicylic
     acid   50-81-7, Vitamin C, biological studies   51-21-8, Fluorouracil
     51-61-6, Dopamine, biological studies   51-63-8, Dextroamphetamine sulfate
     51-98-9, Norethindrone acetate   52-01-7, Spironolactone   52-24-4,
     Thiotepa   52-86-8, Haloperidol   53-36-1, Methylprednisolone Acetate
     54-31-9, Furosemide   55-63-0, Nitroglycerin   57-63-6, Ethinyl estradiol
     58-08-2, Caffeine, biological studies   58-18-4, Methyltestosterone
     58-25-3, Chlordiazepoxide   58-33-3, Promethazine hydrochloride   58-55-9,
     Theophylline, biological studies   58-61-7, Adenosine, biological studies
     58-93-5, Hydrochlorothiazide   59-42-7, Phenylephrine   60-54-8,
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Tetracycline 60-87-7, Promethazine 64-31-3, Morphine Sulfate 67-20-9, Nitrofurantoin 67-92-5, Dicyclomine hydrochloride 68-19-9, Vitamin B12 68-22-4, Norethindrone 71-58-9, Medroxyprogesterone acetate 71-68-1, Hydromorphone hydrochloride 74-79-3, Arginine, biological studies 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-58-4, Ethylmorphine 78-44-4, Carisoprodol 84-02-6, Prochlorperazine maleate 87-08-1, Penicillin V 87-33-2, Isosorbide Dinitrate 89-57-6, Mesalamine 90-82-4, Pseudoephedrine 93-14-1, Guaifenesin 113-45-1, Methylphenidate 113-52-0 113-92-8, Chlorpheniramine maleate 114-07-8, Erythromycin 124-90-3, Oxycodone hydrochloride 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-33-7, Primidone 125-71-3, Dextromethorphan 128-13-2, Ursodiol 129-06-6, Warfarin Sodium 132-17-2, Benzatropine methanesulfonate 143-52-2, Methyldihydromorphinone 143-71-5, Hydrocodone bitartrate 152-11-4, Verapamil hydrochloride 297-76-7, Ethynodiol diacetate 298-46-4, Carbamazepine 298-59-9, Methylphenidate hydrochloride 303-49-1, Clomipramine 315-30-0, Allopurinol 318-98-9, Propranolol Hydrochloride 378-44-9, Betamethasone 379-79-3, Ergotamine Tartrate 437-38-7, Fentanyl 439-14-5, Diazepam 446-86-6, Azathioprine 466-99-9, Hydromorphone 469-62-5, Propoxyphene 509-60-4, Dihydromorphine 514-36-3, Fludrocortisone acetate 541-15-1, Levocarnitine 549-18-8, Amitriptyline hydrochloride 554-13-2, Lithium Carbonate 561-27-3, Diacetylmorphine 595-33-5, Megestrol acetate 604-75-1, Oxazepam 630-93-3, Sodium phenytoin 657-24-9, Metformin 745-65-3, Alprostadil 747-36-4, Hydroxychloroquine sulfate 797-63-7, Levonorgestrel 846-49-1, Lorazepam 846-50-4, Temazepam 894-71-3, Nortriptyline hydrochloride 959-24-0, Sotalol hydrochloride 1134-47-0, Baclofen 1403-66-3, Gentamicin 1404-93-9, Vancomycin hydrochloride 1501-84-4, Rimantadine hydrochloride 1508-65-2, Oxybutynin chloride 1622-61-3, Clonazepam 1665-48-1, Metaxalone 1744-22-5, Riluzole 1951-25-3, Amiodarone 2078-54-8, Propofol 2152-34-3, Pemoline 2375-03-3, Methylprednisolone sodium succinate 4205-91-8 4682-36-4, Orphenadrine citrate 4759-48-2, Isotretinoin 5786-21-0, Clozapine 6202-23-9, Cyclobenzaprine hydrochloride 6493-05-6, Pentoxifylline 6533-00-2, Norgestrel 7280-37-7, Estropipate 7414-83-7, Etidronate disodium 9002-60-2, Adrenocorticotrophic hormone, biological studies 9002-69-1, Relaxin 9005-49-6, Heparin, biological studies 9014-42-0, Thrombopoietin 9039-53-6, Urokinase 9041-08-1, Dalteparin sodium 9041-92-3, .α.1-Protease inhibitor 9080-79-9, Sodium polystyrene sulfonate 10238-21-8, Glyburide 11005-12-2, β-Phytosterol 11056-06-7, Bleomycin 11140-85-5, Glucagon hydrochloride 13311-84-7, Flutamide 13614-98-7, Minocycline hydrochloride 14124-50-6, **Hydrochlorothiazide**-triamterene mixture 14611-52-0, Selegiline hydrochloride 14838-15-4, Phenylpropanolamine 15307-79-6, Diclofenac sodium 15663-27-1, Cisplatin 15686-71-2, Cephalexin 17140-78-2, Propoxyphene napsylate 17560-51-9, Metolazone 18559-94-9, Albuterol 19767-45-4, Mesna 20537-88-6, Amifostine 20830-75-5, Digoxin 21062-37-3D, analogs 21256-18-8, Oxaprozin 21829-25-4, Nifedipine 22071-15-4, Ketoprofen 23031-32-5, Terbutaline sulfate 25316-40-9, Doxorubicin hydrochloride 25322-68-3, Polyethylene glycol 25332-39-2, Trazodone hydrochloride 25614-03-3, Bromocriptine 26159-34-2, Naproxen sodium 26787-78-0, Amoxicillin 27164-46-1, Cefazolin sodium 27314-97-2, Tirapazamine 28860-95-9, Carbidopa 28981-97-7, Alprazolam 29094-61-9, Glipizide 29354-16-3, Thyronine, iodo- 31677-93-7, Bupropion hydrochloride 32222-06-3, Calcitriol 32780-64-6, Labetalol hydrochloride 33069-62-4, Paclitaxel 33286-22-5, Diltiazem hydrochloride 33419-42-0, Etoposide 33564-30-6, Cefoxitin sodium

34552-83-5, Loperamide hydrochloride 34580-13-7, Ketotifen 35189-28-7, Norgestimate 36282-47-0, Tramadol hydrochloride 36505-84-7, Buspirone 36791-04-5, Ribavirin 37296-80-3, Colestipol hydrochloride 38398-32-2, Ganaxolone 41340-25-4, Etodolac 41575-94-4, Carboplatin 42200-33-9, Nadolol 42617-41-4, Activated protein C 42924-53-8, Nabumetone 49562-28-9, Fenofibrate 49842-07-1, Tobramycin sulfate 50370-12-2, Cefadroxil 50700-72-6, Vecuronium bromide 51321-79-0, Sparfosic acid 51481-61-9, Cimetidine 51773-92-3, Mefloquine hydrochloride 52232-67-4, Teriparatide 53885-35-1, Ticlopidine hydrochloride 53994-73-3, Cefaclor 54024-22-5, Desogestrel 54143-56-5, Flecainide acetate 54182-58-0, Sucralfate 54910-89-3, Fluoxetine 54965-24-1, Tamoxifen citrate 55079-83-9, Acitretin 56180-94-0, Acarbose 56238-63-2, Cefuroxime sodium 57109-90-7, Clorazepate dipotassium 57248-88-1, Pamidronate disodium 57852-57-0, Idarubicin hydrochloride 58579-51-4, Anagrelide hydrochloride 58786-99-5, Butorphanol tartrate 59122-46-2, Misoprostol 59703-84-3, Piperacillin sodium 59729-32-7, Citalopram hydrobromide 59865-13-3, Cyclosporin 59989-18-3, Eniluracil 60142-96-3, Gabapentin 60205-81-4, Ipratropium 60748-06-3, Gastrin 17 61718-82-9, Fluvoxamine maleate 62288-83-9, Desmopressin acetate 62571-86-2, Captopril 63074-08-8, Terazosin hydrochloride 63675-72-9, Nisoldipine 64221-86-9, Imipenem 64461-82-1, Tizanidine hydrochloride 64485-93-4, Cefotaxime sodium 64544-07-6, Cefuroxime axetil 65277-42-1, Ketoconazole 65646-68-6, Fenretinide 65807-02-5, Goserelin 66085-59-4, Nimodipine 66104-22-1, Pergolide 66357-35-5, Ranitidine 66722-44-9, Bisoprolol 67889-72-9, Acetaminophen-codeine phosphate mixture 67992-58-9, Sodium ioxaglate 68562-41-4, Mecasermin 68693-11-8, Modafinil 68844-77-9, Astemizole 69655-05-6, Didanosine 70458-96-7, Norfloxacin 70476-82-3, Mitoxantrone hydrochloride 72509-76-3, Felodipine 72558-82-8, Ceftazidime 72956-09-3, Carvedilol 73334-07-3, Iopromide 73573-87-2, Formoterol 73590-58-6, Omeprazole 74103-06-3, Ketorolac 74191-85-8, Doxazosin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

IT 74356-00-6, Cefotetan disodium 74381-53-6, Leuprolide acetate 74469-00-4, Amoxicillin-potassium clavulanate mixture 75330-75-5, Lovastatin 75695-93-1, Isradipine 75706-12-6, Leflunomide 75847-73-3, Enalapril 75970-99-9, Norastemizole 76470-66-1, Loracarbef 76547-98-3, Lisinopril 76584-70-8, Divalproex sodium 76820-74-1, Sodium meglumine ioxaglate 76824-35-6, Famotidine 76963-41-2, Nizatidine 78246-49-8, Paroxetine hydrochloride 78628-80-5, Terbinafine hydrochloride 78755-81-4, Flumazenil 79307-93-0, Azelastine hydrochloride 79350-37-1, Cefixime 79517-01-4, Octreotide acetate 79794-75-5, Loratadine 79902-63-9, Simvastatin 81098-60-4, Cisapride 81103-11-9, Clarithromycin 81129-83-1, Cilastatin sodium 81131-70-6, Pravastatin sodium 81409-90-7, Cabergoline 81627-83-0, M-CSF 82410-32-0, Ganciclovir 82419-36-1, Ofloxacin 82586-52-5, Moexipril hydrochloride 82586-55-8, Quinapril hydrochloride 82626-48-0, Zolpidem 82640-04-8, Raloxifene hydrochloride 82657-92-9, Prourokinase 82752-99-6, Nefazodone hydrochloride 83015-26-3, Tomoxetine 83881-52-1, Cetirizine hydrochloride 83905-01-5, Azithromycin 83928-66-9, Gepirone hydrochloride 84057-84-1, Lamotrigine 84485-00-7, Sibutramine hydrochloride 84625-61-6, Itraconazole 85650-52-8, Mirtazapine 85721-33-1, Ciprofloxacin 86050-77-3, Gadopentetate dimeglumine 86386-73-4, Fluconazole 86541-74-4, Benazepril hydrochloride 87239-81-4, Cefpodoxime proxetil 87333-19-5, Ramipril 87679-37-6, Trandolapril 90357-06-5, Bicalutamide 90566-53-3, Fluticasone 91374-20-8, Ropinirole hydrochloride

91421-42-0, Rubitecan 91832-40-5, Cefdinir 92134-98-0, Fosphenytoin sodium 92339-11-2, Iodixanol 92665-29-7, Cefprozil 93379-54-5, Esatenolol 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 95233-18-4, Atovaquone 95635-56-6, Ranolazine hydrochloride 95896-08-5, Anaritide 96036-03-2, Meropenem 96829-58-2, Orlistat 96946-42-8, Cisatracurium besylate 97240-79-4, Topiramate 97322-87-7, Troglitazone 97519-39-6, Ceftibuten 98048-97-6, Fosinopril 98319-26-7, Finasteride 98418-47-4, Metoprolol succinate 99300-78-4, Venlafaxine hydrochloride 99614-01-4, Ondansetron hydrochloride 100286-90-6, Irinotecan hydrochloride 100286-97-3, Milrinone lactate 100986-85-4, Levofloxacin 103475-41-8, Tepoxalin 103577-45-3, Lansoprazole 104227-87-4, Famciclovir 104632-25-9, Pramipexole dihydrochloride 106266-06-2, Risperidone 106392-12-5, Poloxamer 188 106861-44-3, Mivacurium chloride 107007-99-8, Granisetron hydrochloride 107753-78-6, Zafirlukast 111470-99-6, Amlodipine besylate 111974-72-2, Quetiapine fumarate 112108-01-7, Ecopipam 112529-15-4, Pioglitazone hydrochloride 112573-73-6, Ecadotril 112733-06-9, Zenarestat 113427-24-0, Epoetin alfa 114977-28-5, Docetaxel 115956-13-3, Dolasetron mesylate 116539-59-4, Duloxetine 117976-90-6, Rabeprazole sodium 118390-30-0, Interferon alfacon-1 119302-91-9, Rocuronium bromide 119413-54-6, Topotecan hydrochloride 120011-70-3, Donepezil hydrochloride 120066-54-8, Gadoteridol 120202-66-6, Clopidogrel bisulfate 120511-73-1, Anastrozole 120635-74-7, Cilansetron 121032-29-9, Nelarabine 121181-53-1D, PEGylated 121584-18-7, Valspodar 122111-03-9, Gemcitabine hydrochloride 123122-55-4, Candoxatril 123258-84-4, Itasetron 124584-08-3, Nesiritide 124750-99-8, Losartan potassium 124832-27-5, Valacyclovir hydrochloride 124937-52-6, Tolterodine tartrate 125317-39-7, Vinorelbine tartrate 126544-47-6, Ciclesonide 127254-12-0, Sitafloxacin 127779-20-8, Saquinavir 128298-28-2, Remacemide 128794-94-5, Mycophenolate mofetil 129318-43-0, Alendronate sodium 129580-63-8, Satraplatin 129618-40-2, Nevirapine 129722-12-9, Aripiprazole 130018-77-8, Levocetirizine 130325-35-8, PD 135158 131918-61-1, Paricalcitol 132449-46-8, Lesopitron 132539-06-1, Olanzapine 133107-64-9, Insulin lispro 133737-32-3, Pagoclone 134523-03-8, Atorvastatin calcium 134564-82-2, Befloxatone 134678-17-4, Lamivudine 135062-02-1, Repaglinide 135306-42-2, BW 1555U88 135354-02-8, Xaliproden 137234-62-9, Voriconazole 137281-23-3, Pemetrexed 137862-53-4, Valsartan 138402-11-6, Irbesartan 138531-07-4, Sinapultide 138660-96-5, Sevirumab 139264-17-8, Zolmitriptan 140207-93-8, Pentosan polysulfate sodium 141579-67-1, A 78773 141732-76-5, Exendin-4 142340-99-6, Adefovir dipivoxil 142373-60-2, Tirofiban hydrochloride 142880-36-2, Ilomastat 143201-11-0, Cerivastatin sodium 143388-64-1, Naratriptan hydrochloride 144980-29-0, Repinotan 145040-37-5, Candesartan cilexetil 145202-66-0, Rizatriptan benzoate 145258-61-3, Interferon β1 (human fibroblast protein moiety) 145375-43-5, Mitiglinide 145821-59-6, Tiagabine hydrochloride 145941-26-0, Oprelvekin 146479-72-3 147059-75-4, Trovafloxacin mesylate 147245-92-9, Glatiramer acetate 147536-97-8, Bosentan 148553-50-8, Pregabalin 148883-56-1, Tifacogin 149824-15-7, Ilodecakin 149845-06-7, Saquinavir mesylate 149950-60-7, Emivirine 151035-56-2 151063-30-8, Lisinopril-**hydrochlorothiazide** mixture 151319-34-5, Zaleplon 151767-02-1, Montelukast sodium 152751-57-0, Sevelamer hydrochloride 153168-05-9, Pleconaril 153259-65-5, Cilomilast 153438-49-4, Dapitant 153439-40-8, Fexofenadine hydrochloride 153773-82-1, MK 826 154039-60-8, Marimastat 154248-97-2, Imiglucerase 154361-50-9, Capecitabine 154598-52-4, Efavirenz 155141-29-0, Rosiglitazone maleate

155213-67-5, Ritonavir 156154-37-9, Losartan-**hydrochlorothiazide** mixture 157263-00-8, L 159282 157542-49-9, CS 834 157810-81-6, Indinavir sulfate 159989-65-8, Nelfinavir mesylate 160135-92-2 161814-49-9, Amprenavir 162011-90-7, Rofecoxib 162808-62-0, Caspofungin 164656-23-9, Dutasteride 166089-32-3, Lintuzumab 166374-48-7, CVT 124 166518-60-1, Avasimibe 169148-63-4, NN 304 169590-42-5, Celecoxib 170277-31-3, Infliximab 171228-49-2, Posaconazole 171599-83-0, Sildenafil citrate 178961-24-5, 264W94 179120-92-4, Altinicline 180288-69-1, Trastuzumab **181069-80-7**, ALT 711 181695-72-7, Valdecoxib 182167-03-9, EM 800 183547-57-1, Gantofiban 183552-38-7, Abarelix 185243-69-0, Etanercept 187348-17-0, Edodekin alfa 187523-35-9, BMS 204352 188039-54-5, Palivizumab 188062-50-2, Abacavir sulfate 188627-80-7, Eptifibatide 189013-61-4, 4030W92 192329-42-3, Prinomastat 193079-69-5, Tabimorelin 198153-51-4, Peginterferon alfa-2a 198283-73-7, ABT 594 202138-50-9, Tenofovir disoproxil fumarate 202409-33-4, Etoricoxib 205110-48-1, ABT 773 208538-73-2, FK 463 210101-16-9, Conivaptan 223652-82-2, BMS 284756 332348-12-6, BMS 188667
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

IT **181069-80-7**, ALT 711
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

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AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the composition to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepared from Glu(OBut)NCA and cephalexin hydrochloride.

2002:332011 Document Number 136:355482 Compositions comprising a polypeptide and an active agent. Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randall J. (New River Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2002034237 A1 20020502, 98 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US26142 20010822. PRIORITY: US 2000-2000/642820 20000822.

IT 50-06-6, Phenobarbital, biological studies 50-18-0, Cyclophosphamide 50-35-1, Thalidomide 50-44-2, Mercaptopurine 50-78-2, Acetylsalicylic acid 50-81-7, Vitamin C, biological studies 51-21-8, Fluorouracil 51-61-6, Dopamine, biological studies 51-63-8, Dextroamphetamine sulfate 51-98-9, Norethindrone acetate 52-01-7, Spironolactone 52-24-4, Thiotepa 52-86-8, Haloperidol 53-36-1, Methylprednisolone Acetate 54-31-9, Furosemide 55-63-0, Nitroglycerin 57-63-6, Ethinyl estradiol 58-08-2, Caffeine, biological studies 58-18-4, Methyltestosterone 58-25-3, Chlordiazepoxide 58-33-3, Promethazine hydrochloride 58-55-9, Theophylline, biological studies 58-61-7, Adenosine, biological studies 58-93-5, **Hydrochlorothiazide** 59-42-7, Phenylephrine 60-54-8, Tetracycline 60-87-7, Promethazine 64-31-3, Morphine Sulfate

67-20-9, Nitrofurantoin 67-92-5, Dicyclomine hydrochloride 68-19-9, Vitamin B12 68-22-4, Norethindrone 71-58-9, Medroxyprogesterone acetate 71-68-1, Hydromorphone hydrochloride 74-79-3, Arginine, biological studies 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-58-4, Ethylmorphine 78-44-4, Carisoprodol 84-02-6, Prochlorperazine maleate 87-08-1, Penicillin V 87-33-2, Isosorbide Dinitrate 89-57-6, Mesalamine 90-82-4, Pseudoephedrine 93-14-1, Guaifenesin 113-45-1, Methylphenidate 113-52-0 113-92-8, Chlorpheniramine maleate 114-07-8, Erythromycin 124-90-3, Oxycodone hydrochloride 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-33-7, Primidone 125-71-3, Dextromethorphan 128-13-2, Ursodiol 129-06-6, Warfarin Sodium 132-17-2, Benzatropine methanesulfonate 132-22-9, Chlorpheniramine 143-52-2, Methyldihydromorphinone 143-71-5, Hydrocodone bitartrate 152-11-4, Verapamil hydrochloride 297-76-7, Ethynodiol diacetate 298-46-4, Carbamazepine 298-59-9, Methylphenidate hydrochloride 303-49-1, Clomipramine 315-30-0, Allopurinol 318-98-9, Propranolol Hydrochloride 378-44-9, Betamethasone 379-79-3, Ergotamine Tartrate 437-38-7, Fentanyl 439-14-5, Diazepam 446-86-6, Azathioprine 466-99-9, Hydromorphone 469-62-5, Propoxyphene 509-60-4, Dihydromorphine 514-36-3, Fludrocortisone acetate 541-15-1, Levocarnitine 549-18-8, Amitriptyline hydrochloride 554-13-2, Lithium Carbonate 561-27-3, Diacetylmorphine 595-33-5, Megestrol acetate 604-75-1, Oxazepam 630-93-3, Sodium phenytoin 657-24-9, Metformin 745-65-3, Alprostadil 747-36-4, Hydroxychloroquine sulfate 797-63-7, Levonorgestrel 846-49-1, Lorazepam 846-50-4, Temazepam 894-71-3, Nortriptyline hydrochloride 959-24-0, Sotalol hydrochloride 1134-47-0, Baclofen 1403-66-3, Gentamicin 1404-93-9, Vancomycin hydrochloride 1501-84-4, Rimantadine hydrochloride 1508-65-2, Oxybutynin chloride 1622-61-3, Clonazepam 1665-48-1, Metaxalone 1744-22-5, Riluzole 1951-25-3, Amiodarone 2078-54-8, Propofol 2152-34-3, Pemoline 2375-03-3, Methylprednisolone sodium succinate 4205-91-8 4682-36-4, Orphenadrine citrate 4759-48-2, Isotretinoin 5786-21-0, Clozapine 6202-23-9, Cyclobenzaprine hydrochloride 6493-05-6, Pentoxifylline 6533-00-2, Norgestrel 7280-37-7, Estropipate 7414-83-7, Etidronate disodium 9002-60-2, Adrenocorticotrophic hormone, biological studies 9002-69-1, Relaxin 9005-49-6, Heparin, biological studies 9014-42-0, Thrombopoietin 9039-53-6, Urokinase 9041-08-1, Dalteparin sodium 9041-92-3, .α.1-Protease inhibitor 9080-79-9, Sodium polystyrene sulfonate 10238-21-8, Glyburide 11005-12-2, β-Phytosterol 11056-06-7, Bleomycin 11140-85-5, Glucagon hydrochloride 13311-84-7, Flutamide 13614-98-7, Minocycline hydrochloride 14124-50-6, **Hydrochlorothiazide**-triamterene mixture 14611-52-0, Selegiline hydrochloride 14838-15-4, Phenylpropanolamine 15307-79-6, Diclofenac sodium 15663-27-1, Cisplatin 15686-71-2, Cephalexin 17140-78-2, Propoxyphene napsylate 17560-51-9, Metolazone 18559-94-9, Albuterol 19767-45-4, Mesna 20537-88-6, Amifostine 20830-75-5, Digoxin 21062-37-3D, analogs 21256-18-8, Oxaprozin 21829-25-4, Nifedipine 22071-15-4, Ketoprofen 23031-32-5, Terbutaline sulfate 25316-40-9, Doxorubicin hydrochloride 25322-68-3, Polyethylene glycol 25332-39-2, Trazodone hydrochloride 25614-03-3, Bromocriptine 26159-34-2, Naproxen sodium 26787-78-0, Amoxicillin 27164-46-1, Cefazolin sodium 27314-97-2, Tirapazamine 28860-95-9, Carbidopa 28981-97-7, Alprazolam 29094-61-9, Glipizide 29354-16-3, Thyronine, iodo- 31677-93-7, Bupropion hydrochloride 32222-06-3, Calcitriol 32780-64-6, Labetalol hydrochloride 33069-62-4, Paclitaxel 33286-22-5, Diltiazem hydrochloride 33419-42-0, Etoposide 33564-30-6, Cefoxitin sodium 34552-83-5, Loperamide hydrochloride 34580-13-7, Ketotifen 35189-28-7,

Norgestimate 36282-47-0, Tramadol hydrochloride 36505-84-7, Buspirone 36791-04-5, Ribavirin 37296-80-3, Colestipol hydrochloride 38398-32-2, Ganaxolone 41340-25-4, Etodolac 41575-94-4, Carboplatin 42200-33-9, Nadolol 42617-41-4, Activated protein C 42924-53-8, Nabumetone 49562-28-9, Fenofibrate 49842-07-1, Tobramycin sulfate 50370-12-2, Cefadroxil 50700-72-6, Vecuronium bromide 51321-79-0, Sparfosic acid 51481-61-9, Cimetidine 51773-92-3, Mefloquine hydrochloride 52232-67-4, Teriparatide 53885-35-1, Ticlopidine hydrochloride 53994-73-3, Cefaclor 54024-22-5, Desogestrel 54143-56-5, Flecainide acetate 54182-58-0, Sucralfate 54910-89-3, Fluoxetine 54965-24-1, Tamoxifen citrate 55079-83-9, Acitretin 56180-94-0, Acarbose 56238-63-2, Cefuroxime sodium 57109-90-7, Clorazepate dipotassium 57248-88-1, Pamidronate disodium 57852-57-0, Idarubicin hydrochloride 58579-51-4, Anagrelide hydrochloride 58786-99-5, Butorphanol tartrate 59122-46-2, Misoprostol 59703-84-3, Piperacillin sodium 59729-32-7, Citalopram hydrobromide 59865-13-3, Cyclosporin 59989-18-3, Eniluracil 60142-96-3, Gabapentin 60205-81-4, Ipratropium 60748-06-3, Gastrin 17 61718-82-9, Fluvoxamine maleate 62288-83-9, Desmopressin acetate 62571-86-2, Captopril 63074-08-8, Terazosin hydrochloride 63675-72-9, Nisoldipine 64221-86-9, Imipenem 64461-82-1, Tizanidine hydrochloride 64485-93-4, Cefotaxime sodium 64544-07-6, Cefuroxime axetil 65277-42-1, Ketoconazole 65646-68-6, Fenretinide 65807-02-5, Goserelin 66085-59-4, Nimodipine 66104-22-1, Pergolide 66357-35-5, Ranitidine 66722-44-9, Bisoprolol 67889-72-9, Acetaminophen-codeine phosphate mixture 67992-58-9, Sodium ioxaglate 68562-41-4, Mecasermin 68693-11-8, Modafinil 68844-77-9, Astemizole 69655-05-6, Didanosine 70458-96-7, Norfloxacin 70476-82-3, Mitoxantrone hydrochloride 72509-76-3, Felodipine 72558-82-8, Ceftazidime 72956-09-3, Carvedilol 73334-07-3, Iopromide 73573-87-2, Formoterol 73590-58-6, Omeprazole 74103-06-3, Ketorolac
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(compns. comprising a polypeptide and an active agent)

IT 74191-85-8, Doxazosin 74356-00-6, Cefotetan disodium 74381-53-6, Leuprolide acetate 74469-00-4, Amoxicillin-potassium clavulanate mixture 75330-75-5, Lovastatin 75695-93-1, Isradipine 75706-12-6, Leflunomide 75847-73-3, Enalapril 75970-99-9, Norastemizole 76470-66-1, Loracarbef 76547-98-3, Lisinopril 76584-70-8, Divalproex sodium 76820-74-1, Sodium meglumine ioxaglate 76824-35-6, Famotidine 76963-41-2, Nizatidine 78246-49-8, Paroxetine hydrochloride 78628-80-5, Terbinafine hydrochloride 78755-81-4, Flumazenil 79307-93-0, Azelastine hydrochloride 79350-37-1, Cefixime 79517-01-4, Octreotide acetate 79794-75-5, Loratadine 79902-63-9, Simvastatin 81098-60-4, Cisapride 81103-11-9, Clarithromycin 81129-83-1, Cilastatin sodium 81131-70-6, Pravastatin sodium 81409-90-7, Cabergoline 81627-83-0, M-CSF 82410-32-0, Ganciclovir 82419-36-1, Ofloxacin 82586-52-5, Moexipril hydrochloride 82586-55-8, Quinapril hydrochloride 82626-48-0, Zolpidem 82640-04-8, Raloxifene hydrochloride 82657-92-9, Prourokinase 82752-99-6, Nefazodone hydrochloride 83015-26-3, Tomoxetine 83881-52-1, Cetirizine hydrochloride 83905-01-5, Azithromycin 83928-66-9, Gepirone hydrochloride 84057-84-1, Lamotrigine 84485-00-7, Sibutramine hydrochloride 84625-61-6, Itraconazole 85650-52-8, Mirtazapine 85721-33-1, Ciprofloxacin 86050-77-3, Gadopentetate dimeglumine 86386-73-4, Fluconazole 86541-74-4, Benazepril hydrochloride 87239-81-4, Cefpodoxime proxetil 87333-19-5, Ramipril 87679-37-6, Trandolapril 90357-06-5, Bicalutamide 90566-53-3, Fluticasone 91374-20-8, Ropinirole hydrochloride 91421-42-0, Rubitecan 91832-40-5, Cefdinir 92134-98-0, Fosphenytoin

sodium 92339-11-2, Iodixanol 92665-29-7, Cefprozil 93379-54-5, Esatenolol 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 95233-18-4, Atovaquone 95635-56-6, Ranolazine hydrochloride 95896-08-5, Anaritide 96036-03-2, Meropenem 96829-58-2, Orlistat 96946-42-8, Cisatracurium besylate 97240-79-4, Topiramate 97322-87-7, Troglitazone 97519-39-6, Ceftibuten 98048-97-6, Fosinopril 98319-26-7, Finasteride 98418-47-4, Metoprolol succinate 99300-78-4, Venlafaxine hydrochloride 99614-01-4, Ondansetron hydrochloride 100286-90-6, Irinotecan hydrochloride 100286-97-3, Milrinone lactate 100986-85-4, Levofloxacin 103475-41-8, Tepoxalin 103577-45-3, Lansoprazole 104227-87-4, Famciclovir 104632-25-9, Pramipexole dihydrochloride 106266-06-2, Risperidone 106392-12-5, Poloxamer 188 106861-44-3, Mivacurium chloride 107007-99-8, Granisetron hydrochloride 107753-78-6, Zafirlukast 111470-99-6, Amlodipine besylate 111974-72-2, Quetiapine fumarate 112108-01-7, Ecopipam 112529-15-4, Pioglitazone hydrochloride 112573-73-6, Ecadotril 112733-06-9, Zenarestat 113427-24-0, Epoetin alfa 114977-28-5, Docetaxel 115956-13-3, Dolasetron mesylate 116539-59-4, Duloxetine 117976-90-6, Rabeprazole sodium 118390-30-0, Interferon alfacon-1 119302-91-9, Rocuronium bromide 119413-54-6, Topotecan hydrochloride 120011-70-3, Donepezil hydrochloride 120066-54-8, Gadoteridol 120202-66-6, Clopidogrel bisulfate 120511-73-1, Anastrozole 120635-74-7, Cilansetron 121032-29-9, Nelarabine 121181-53-1D, PEGylated 121584-18-7, Valspodar 122111-03-9, Gemcitabine hydrochloride 123122-55-4, Candoxatril 123258-84-4, Itasetron 124584-08-3, Nesiritide 124750-99-8, Losartan potassium 124832-27-5, Valacyclovir hydrochloride 124937-52-6, Tolterodine tartrate 125317-39-7, Vinorelbine tartrate 126544-47-6, Ciclesonide 127254-12-0, Sitafloxacin 127779-20-8, Saquinavir 128298-28-2, Remacemide 128794-94-5, Mycophenolate mofetil 129318-43-0, Alendronate sodium 129580-63-8, Satraplatin 129618-40-2, Nevirapine 129722-12-9, Aripiprazole 130018-77-8, Levocetirizine 130325-35-8, PD 135158 131918-61-1, Paricalcitol 132449-46-8, Lesopitron 132539-06-1, Olanzapine 133107-64-9, Insulin lispro 133737-32-3, Pagoclone 134523-03-8, Atorvastatin calcium 134564-82-2, Befloxatone 134678-17-4, Lamivudine 135062-02-1, Repaglinide 135306-42-2, BW 1555U88 135354-02-8, Xaliproden 137234-62-9, Voriconazole 137281-23-3, Pemetrexed 137862-53-4, Valsartan 138402-11-6, Irbesartan 138531-07-4, Sinapultide 138660-96-5, Sevirumab 139264-17-8, Zolmitriptan 140207-93-8, Pentosan polysulfate sodium 141579-67-1, A 78773 141732-76-5, Exendin-4 142340-99-6, Adefovir dipivoxil 142373-60-2, Tirofiban hydrochloride 142880-36-2, Ilomastat 143201-11-0, Cerivastatin sodium 143388-64-1, Naratriptan hydrochloride 144980-29-0, Repinotan 145040-37-5, Candesartan cilexetil 145202-66-0, Rizatriptan benzoate 145258-61-3, Interferon β1 (human fibroblast protein moiety) 145375-43-5, Mitiglinide 145821-59-6, Tiagabine hydrochloride 145941-26-0, Oprelvekin 146479-72-3 147059-75-4, Trovafloxacin mesylate 147245-92-9, Glatiramer acetate 147536-97-8, Bosentan 148553-50-8, Pregabalin 148883-56-1, Tifacogin 149824-15-7, Ilodecakin 149845-06-7, Saquinavir mesylate 149950-60-7, Emivirine 151035-56-2 151063-30-8, Lisinopril-**hydrochlorothiazide** mixture 151319-34-5, Zaleplon 151767-02-1, Montelukast sodium 152751-57-0, Sevelamer hydrochloride 153168-05-9, Pleconaril 153259-65-5, Cilomilast 153438-49-4, Dapitant 153439-40-8, Fexofenadine hydrochloride 153773-82-1, MK 826 154039-60-8, Marimastat 154248-97-2, Imiglucerase 154361-50-9, Capecitabine 154598-52-4, Efavirenz 155141-29-0, Rosiglitazone maleate 155213-67-5, Ritonavir 156154-37-9, Losartan-**hydrochlorothiazide**

mixture 157263-00-8, L 159282 157542-49-9, CS 834 157810-81-6, Indinavir sulfate 159989-65-8, Nelfinavir mesylate 160135-92-2 161814-49-9, Amprenavir 162011-90-7, Rofecoxib 162808-62-0, Caspofungin 164656-23-9, Dutasteride 166089-32-3, Lintuzumab 166374-48-7, CVT 124 166518-60-1, Avasimibe 169148-63-4, NN 304 169590-42-5, Celecoxib 170277-31-3, Infliximab 171228-49-2, Posaconazole 171599-83-0, Sildenafil citrate 178961-24-5, 264W94 179120-92-4, Altinicline 180288-69-1, Trastuzumab **181069-80-7**, ALT 711 181695-72-7, Valdecoxib 182167-03-9, EM 800 183547-57-1, Gantofiban 183552-38-7, Abarelix 185243-69-0, Etanercept 187348-17-0, Edodekin alfa 187523-35-9, BMS 204352 188039-54-5, Palivizumab 188062-50-2, Abacavir sulfate 188627-80-7, Eptifibatide 189013-61-4, 4030W92 192329-42-3, Prinomastat 193079-69-5, Tabimorelin 198153-51-4, Peginterferon alfa-2a 198283-73-7, ABT 594 202138-50-9, Tenofovir disoproxil fumarate 202409-33-4, Etoricoxib 205110-48-1, ABT 773 208538-73-2, FK 463 210101-16-9, Conivaptan 223652-82-2, BMS 284756 332348-12-6, BMS 188667
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

IT **181069-80-7**, ALT 711
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

L6 ANSWER 3 OF 3 USPATFULL on STN

AB Provided are compounds of the formula (and pharmaceutically acceptable salts thereof): ##STR1##

wherein:

R is hydrogen, methyl, hydroxymethyl or α-hydroxyethyl;

R.sup.1 and R.sup.2 are independently selected from hydrogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 hydroxyalkyl, C.sub.3-C.sub.8 cycloalkyl, C.sub.1-C.sub.6 alkenyl, C.sub.1-C.sub.6 alkynyl, amino, monoalkylamino, dialkylaminoalkyl, and pyrrolidin-1-ylalkyl; and Y is selected from the group consisting of C.sub.1-C.sub.6 alkyl, substituted and unsubstituted aryl; with the provisos that: (a) if Y is aryl, then at least one of R.sup.1 and R.sup.2 is other than hydrogen, and (b) if R.sup.2 is hydrogen R.sup.1 is other than methyl.

Also provided are pharmaceutical compositions containing the compounds, and methods for the preparation of the compounds. The compounds are useful, among other things, as prodrugs which can be converted under acidic conditions to thiazolium agents. The compounds can be administered to mammals, including humans, for treatment of various indications.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

2005:17345 Dihydrothiazine prodrugs of thiazolium agents.
Reinhard, Emily, Ridgewood, NJ, UNITED STATES
Katten, Elliot, Flushing, NY, UNITED STATES
US 2005014747 A1 20050120
APPLICATION: US 2004-824848 A1 20040415 (10)
PRIORITY: US 2003-463807P 20030418 (60)
DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . is known in the art. Among diuretics, preferred examples

include Furosemide, Bumetanide, Torsemide, Ethacrynic acid, Azosemide, Muzolimine, Piretanide, Tripamide and **Hydrochlorothiazide**, which are administered in effective amounts as is known in the art. Examples of beta adrenergic antagonists include Metoprolol, Carvedilol,. . .

IT **341028-37-3** 787621-18-5
(preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for hypertension, diastolic dysfunction, heart failure, and reduced vascular compliance)

IT **341028-37-3**
(preparation of dihydrothiazine prodrugs of thiazolium agents and their pharmaceutical use for hypertension, diastolic dysfunction, heart failure, and reduced vascular compliance)

=>

FILE 'HCAPLUS' ENTERED AT 20:10:30 ON 04 JAN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'USPATFULL' ENTERED AT 20:10:30 ON 04 JAN 2006

FILE 'USPAT2' ENTERED AT 20:10:30 ON 04 JAN 2006

=> s l5(p)l10
L12 37 L5(P) L10

=> dup rem l12
PROCESSING COMPLETED FOR L12
L13 37 DUP REM L12 (0 DUPLICATES REMOVED)

=> d l13 cbib 1-37

L13 ANSWER 1 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2005:1071684 Document No. 143:415866 The angiotensin II receptor antagonist telmisartan reduces urinary albumin excretion in patients with isolated systolic hypertension: results of a randomized, double-blind, placebo-controlled trial. Vogt, Liffert; Navis, Gerjan; Koester, Juergen; Manolis, Athanasios J.; Reid, John L.; de Zeeuw, Dick (Departments of Clinical Pharmacology and Internal Medicine, Division of Nephrology, Uniiv. Groningen, Groningen, 9713 GZ, Neth.). Journal of Hypertension, 23(11), 2055-2061 (English) 2005. CODEN: JOHYD3. ISSN: 0263-6352. Publisher: Lippincott Williams & Wilkins.

L13 ANSWER 2 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2005:1016166 Antihypertensive efficacy and tolerability of two fixed-dose combinations of valsartan and hydrochlorothiazide compared with valsartan monotherapy in patients with stage 2 or 3 systolic hypertension: an 8-week, randomized, double-blind, parallel-group trial. Lacourciere, Yves; Poirier, Luc; Hebert, Daniel; Assouline, Linda; Stolt, Pelle; Rehel, Bonita; Khder, Yasser (Centre Hospitalier de l'Universite Laval (CHUQ), Saint-Foy, QC, Can.). Clinical Therapeutics, 27(7), 1013-1021 (English) 2005. CODEN: CLTHDG. ISSN: 0149-2918. Publisher: Excerpta Medica, Inc..

L13 ANSWER 3 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2005:274548 Document No. 143:19602 Evaluation of long-term efficacy and acceptability of indapamide SR in elderly hypertensive patients. Leonetti, Gastone; Emeriau, Jean-Paul; Khauf, Heinrich; Pujadas, Juan Ocon; Calvo-Gomez, Carlos; Abate, Giuseppe (European Study Investigators, Department of Cardiology, Ospedale San Luca, Milan, Italy). Current Medical Research and Opinion, 21(1), 37-46 (English) 2005. CODEN: CMROCX. ISSN: 0300-7995. Publisher: LibraPharm Ltd..

L13 ANSWER 4 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2004:873588 Document No. 142:189841 Telmisartan/hydrochlorothiazide combination therapy in the treatment of essential hypertension. Schmieder, Roland E. (Department of Medicine IV, University Erlangen-Nuremberg, Erlangen, 91054, Germany). Expert Opinion on Pharmacotherapy, 5(11), 2303-2310 (English) 2004. CODEN: EOPHF7. ISSN:

1465-6566. Publisher: Ashley Publications Ltd..

L13 ANSWER 5 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2004:514595 Document No. 141:82025 Angiotensin II receptor antagonist telmisartan in **isolated systolic hypertension** (ARAMIS) study: Efficacy and safety of telmisartan 20, 40 or 80 mg versus **hydrochlorothiazide** 12.5 mg or placebo. Manolis, Athanasios J.; Reid, John L.; De Zeeuw, Dick; Murphy, Michael B.; Seewaldt-Becker, Elke; Koester, Juergen (ARAMIS Study Group, Tzanio General Hospital, Piraeus, Greece). Journal of Hypertension, 22(5), 1033-1037 (English) 2004. CODEN: JOHYD3. ISSN: 0263-6352. Publisher: Lippincott Williams & Wilkins.

L13 ANSWER 6 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2004:367018 Document No. 140:385768 Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. Staessen, Jan A.; Thijs, Lutgarde; Fagard, Robert; Celis, Hilde; Birkenhaeger, Willem H.; Bulpitt, Christopher J.; de Leeuw, Peter W.; Fletcher, Astrid E.; Forette, Francoise; Leonetti, Gastone; McCormack, Patricia; Nachev, Choudomir; O'Brien, Eoin; Rodicio, Jose L.; Rosenfeld, Joseph; Sarti, Cinzia; Tuomilehto, Jaakko; Webster, John; Yodfat, Yair; Zanchetti, Alberto (Department of Molecular and Cardiovascular Research, University of Leuven, Belg.). Journal of Hypertension, 22(4), 847-857 (English) 2004. CODEN: JOHYD3. ISSN: 0263-6352. Publisher: Lippincott Williams & Wilkins.

L13 ANSWER 7 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2004:923172 Document No. 142:308810 Candesartan cilexetil in cardiovascular disease. Ross, Amy; Papademetriou, Vasilios (Department of Veterans Affairs Medical Center, Georgetown University, Washington, DC, 20422, USA). Expert Review of Cardiovascular Therapy, 2(6), 829-835 (English) 2004. CODEN: ERCTAS. ISSN: 1477-9072. Publisher: Future Drugs Ltd..

L13 ANSWER 8 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2004:687892 Document No. 142:106939 Once-daily eprosartan mesylate in the treatment of elderly patients with isolated systolic hypertension: data from a 13-week double-blind, placebo-controlled, parallel, multicenter study. Punzi, H. A.; Punzi, C. F. (Trinity Hypertension Research Institute, Punzi Medical Center, Carrollton, TX, USA). Journal of Human Hypertension, 18(9), 655-661 (English) 2004. CODEN: JHHYEN. ISSN: 0950-9240. Publisher: Nature Publishing Group.

L13 ANSWER 9 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2004:10839 Document No. 140:53093 A randomized, double-blind, active-controlled, parallel-group comparison of valsartan and amlodipine in the treatment of isolated systolic hypertension in elderly patients: the Val-Syst study. Malacco, Ettore; Vari, Natale; Capuano, Vincenzo; Spagnuolo, Vitaliano; Borgnino, Carlo; Palatini, Paolo (Val-Syst Investigators, Division of Internal Medicine, Ospedale L. Sacco, University of Milan, Milan, Italy). Clinical Therapeutics, 25(11), 2765-2780 (English) 2003. CODEN: CLTHDG. ISSN: 0149-2918. Publisher: Excerpta Medica, Inc..

L13 ANSWER 10 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2003:990224 Document No. 140:245834 Lercanidipine: a review of its efficacy in the management of hypertension. Bang, Lynne M.; Chapman, Therese M.; Goa, Karen L. (Adis International Limited, Auckland, N. Z.). Drugs,

63(22), 2449-2472 (English) 2003. CODEN: DRUGAY. ISSN: 0012-6667. Publisher: Adis International Ltd..

L13 ANSWER 11 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2003:554545 Document No. 139:207443 Comparison of the blood pressure-lowering effects and tolerability of losartan- and amlodipine-based regimens in patients with isolated systolic hypertension. Volpe, Massimo; Junren, Zhu; Maxwell, Thomas; Rodriguez, Aldo; Gamboa, Raul; Gomez-Fernandez, Pablo; Ortega-Gonzalez, Gines; Matadamas, Norberta; Rodriguez, Freddy; Dass, Badal; Kyle, Chris; Clarysse, Laurent; Bryce, Alfonso; Moreno-Heredia, Ernesto; Germano, Giuseppe; Gilles, Leen; Smith, Ronald D.; Sanderson, John E. (CDSP-944 Study Group, Universita degli Studi di Roma "La Sapienza", Rome, Italy). Clinical Therapeutics, 25(5), 1469-1489 (English) 2003. CODEN: CLTHDG. ISSN: 0149-2918. Publisher: Excerpta Medica, Inc..

L13 ANSWER 12 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2003:446881 Document No. 139:94667 Clinical role of natrilix SR in the treatment of at-risk hypertensive patients. Ambrosioni, Ettore; Veronesi, Maddalena (Universita degli Studi di Bologna, Policlinico S. Orsola-Malpighi, Bologna, 40138, Italy). Journal of Hypertension, 21(Suppl. 1), S13-S17 (English) 2003. CODEN: JOHYD3. ISSN: 0263-6352. Publisher: Lippincott Williams & Wilkins.

L13 ANSWER 13 OF 37 USPATFULL on STN
2002:8500 Vasopeptidase Inhibitors to treat isolated systolic hypertension.
Reeves, Richard A., Pennington, NJ, UNITED STATES
Wolf, Robert A., Newton, PA, UNITED STATES
Chang, Paul I., Doylestown, PA, UNITED STATES
US 2002004500 A1 20020110
APPLICATION: US 2001-819549 A1 20010328 (9)
PRIORITY: US 2000-194499P 20000403 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L13 ANSWER 14 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2002:743966 Quality of life on randomized treatment for isolated systolic hypertension: results from the Syst-Eur Trial. Fletcher, Astrid E.; Bulpitt, Christopher J.; Thijs, Lutgarde; Tuomilehto, Jaakko; Antikainen, Riitta; Bossini, Alfredo; Browne, John; Duggan, Joseph; Kawecka-Jaszcz, Kalina; Kivinen, Paula; Sarti, Cinzia; Terzoli, Laura; Staessen, Jan A. (London School of Hygiene & Tropical Medicine, Centre fro Ageing and Public Health, London, UK). Journal of Hypertension, 20(10), 2069-2079 (English) 2002. CODEN: JOHYD3. ISSN: 0263-6352. Publisher: Lippincott Williams & Wilkins.

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2002:612980 Document No. 138:198354 Pharmacological prevention and regression of arterial remodeling in a rat model of isolated systolic hypertension. Dao, Huy Hao; Essalihi, Rachida; Graillon, Jean-Francois; Lariviere, Richard; De Champlain, Jacques; Moreau, Pierre (Faculty of Pharmacy, Universite de Montreal, Montreal, QC, H3C 3J7, Can.). Journal of Hypertension, 20(8), 1597-1606 (English) 2002. CODEN: JOHYD3. ISSN: 0263-6352. Publisher: Lippincott Williams & Wilkins.

L13 ANSWER 16 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2002:729887 Document No. 137:304548 Effects of Losartan on cardiovascular

morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy. A Lorsartan Intervention for Endpoint Reduction (LIFE) substudy. Kjeldsen, Sverre E.; Dahloef, Bjoern; Devereux, Richard B.; Julius, Stevo; Aurup, Peter; Eldelman, Jonathan; Beevers, Gareth; de Faire, Ulf; Fyhrquist, Frej; Ibsen, Hans; Kirstianson, Krister; Lederballe-Pedersen, Ole; Lindholm, Lars H.; Nieminen, Markku S.; Omvik, Per; Oparil, Suzanne; Snapinn, Steven; Wedel, Hans (LIFE Study Group, Department of Cardiology, Ullevaal Hospital, Oslo, N-0407, Norway). JAMA, the Journal of the American Medical Association, 288(12), 1491-1498 (English) 2002. CODEN: JAMAAP. ISSN: 0098-7484. Publisher: American Medical Association.

L13 ANSWER 17 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2002:933194 Document No. 139:110841 Are Antihypertensive Agents Protective Against Dementia? A Review of Clinical and Preclinical Data. Frishman, William H. (Dep. of Med., New York Med. Coll. and Westchester Med. Cent., Valhalla, NY, 10595, USA). Heart Disease, 4(6), 380-386 (English) 2002. CODEN: HTDSFE. ISSN: 1521-737X. Publisher: Lippincott Williams & Wilkins.

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2002:694413 Document No. 137:241941 Clinical results with bisoprolol 2.5 mg/hydrochlorothiazide 6.25 mg combination in systolic hypertension in the elderly. Benetos, Athanase; Adamopoulos, Chris; Argyriadis, Pandelis; Bean, Kathy; Consoli, Silla; Safar, Michel (IPC Center, INSERM U258, Paris, 75116, Fr.). Journal of Hypertension, 20(Suppl. 1), S21-S25 (English) 2002. CODEN: JOHYD3. ISSN: 0263-6352. Publisher: Lippincott Williams & Wilkins.

L13 ANSWER 19 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2002:694412 Document No. 137:241579 Fixed low-dose combination in first-line treatment of hypertension. Prisant, L. Michael (Hypertension Unit, BBR-6521, Section of Cardiology, Medical College of Georgia, Augusta, GA, 30912-3105, USA). Journal of Hypertension, 20(Suppl. 1), S11-S19 (English) 2002. CODEN: JOHYD3. ISSN: 0263-6352. Publisher: Lippincott Williams & Wilkins.

L13 ANSWER 20 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2001:747597 Document No. 135:267248 Vasopeptidase inhibitors, alone or with other agents, for the treatment of isolated systolic hypertension. Reeves, Richard A.; Wolf, Robert A.; Chang, Paul I. (Bristol-Myers Squibb Co., USA). PCT Int. Appl. WO 2001074348 A2 20011011, 16 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US8240 20010315. PRIORITY: US 2000-PV194499 20000403.

L13 ANSWER 21 OF 37 HCAPLUS COPYRIGHT 2006 ACS on STN
2002:163651 Document No. 136:303481 Dihydropyridine calcium-channel blockers for antihypertensive treatment in older patients - evidence from the systolic hypertension in Europe trial. Staessen, Jan A.; Thijs, Lutgarde; Celis, Hilde; Gasowski, Jerzy; Wang, Ji G.; Fagard, Robert H.

(Laboratorium Hypertensie, Louvain, B-3000, Belg.). SAMJ, 91(12), 1060-1068 (English) 2001. CODEN: SAMJEJ. ISSN: 0256-9574. Publisher: SA Medical Association Health and Medical Publishing.

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